IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	
MANDRUSOV, Evgenia, et al.	**Group Art Unit:** 1792
Serial No.: 10/678,763	**Examiner:** Cameron, Erma C.
Filed: 2 October 2003	
For: METHOD OF MANUFACTURING A STENT COATING AND A METHOD OF USING THE STENT	

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

This appeal brief is submitted pursuant to the Notice of Appeal that was filed on 10 January 2008 in response to the Final Office Action mailed on 17 October 2007 in which all pending and not withdrawn claims were rejected.

REAL PARTY IN INTEREST

The real party in interest with regard to this appeal is Abbott Cardiovascular Systems, Inc., with its primary place of business at 3200 Lakeside Drive, Santa Clara, California 95054. The present application is a division of application number 09/846,498, now Pat. No. 6,660,034. The assignment by the inventors in Pat. No. 6,660,034 to Advanced Cardiovascular Systems was recorded at Reel/Frame

011798/0481 on 30 April 2001. Abbott Cardiovascular System, Inc. purchased the vascular device division and all relevant intellectual property including the instant application of Advanced Cardiovascular Systems, Inc., a.k.a. Guidant Corporation, in April 2006.

RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences related to or that might have any bearing, direct or indirect, on the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 1-22 are canceled and claims 23-77 are pending. Claims 23, 30-32, 45, 56-60, 64-66 are finally rejected, and form the subject of this appeal. All other pending claims, namely claims 24-29, 33-34, 46-55, 61-63, and 67-77, are withdrawn.

STATUS OF AMENDMENTS

The Amendment filed 24 April 2007, in reply to the non-final Office Action of 25 January 2007, was entered.

SUMMARY OF CLAIMED SUBJECT MATTER

Claims 23, 56, and 64 are the only independent claims on appeal.

Independent claim 23 is directed to a method of manufacturing a drug delivery coating for a stent (10). The method comprises forming a first coating (28) on the inner surface (20) of the stent, the first coating including an angiogenic substance and configured to release the angiogenic substance in the vessel (see Figures 3, 5B and 5C; and Specification page 14, lines 9-17, and page 18, line 14 through page 19, line 8). The method further comprises forming a second coating (32) on the outer surface (18) of the stent (10), the second coating including a therapeutic substance capable of inhibiting migration or proliferation of smooth muscle cells and configured to apply the therapeutic substance to the wall of the vessel (see Figures 3 and 5D; and Specification page 16, lines 3, 4, 15-17, and page 19, line 18 through page 20, line 7). The outer surface is free from the first coating including the angiogenic substance and the inner surface is free from the second coating including the therapeutic substance (see Specification, page 15, lines 3-7 and page 16, lines 3-8).

Independent claim 56 is directed to a method of manufacturing a drug delivery coating for a stent (10), the stent including a tubular body having an outer surface (18) and an inner surface (20). The method of claim 56 comprises applying a first composition (28) to the inner surface (20) of the stent (10), the first composition including a first therapeutic substance capable of facilitating angiogenesis (see Figures 3, 5B and 5C; and Specification page 14, lines 9-17, and page 18, line 14 through page 19, line 8). The method of claim 56 further comprises applying a second composition (32) to the outer surface (18) of the stent, the second composition including a second therapeutic substance, the second therapeutic substance capable of inhibiting migration or proliferation of smooth muscle cells (see Figures 3 and 5D; and Specification page 16, lines 3, 4, 15-17, and page 19, line 18 through page 20, line 7). In claim 56, the outer surface is free from the first therapeutic substance and the inner surface is free from the second therapeutic substance (see Specification, page 15, lines 3-7 and page 16, lines 3-8).

Independent claim 64 is directed to a method of manufacturing a coating for a stent (10), the stent including a tubular body having an outer surface (18) and an inner surface (20). The method of claim 64 comprises temporarily placing a cover on the inner surface (20) of the stent, applying a first composition to the outer surface (18) of the stent to form a first coating (32), covering the first coating on the outer surface of the stent, and applying a second composition to the inner surface (20) of the stent to form a second coating (28) (see Specification, page 15, lines 3-7 and page 16, lines 3-8).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claim 64 is unpatentable under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Whether claims 23, 32, 56, and 60 are unpatentable under 35 U.S.C. §102(e) as being anticipated by Ragheb et al., U.S. Pat. No. 6,299,604 (Evidence Appendix, Exhibit. A, hereinafter "Ragheb").

Whether claims 23, 45, 56, 58, and 59 are unpatentable under 35 U.S.C. §102(e) as being anticipated by Weber, U.S. Pat. No. 6,517,888 (Evidence App., Ex. B).

Whether claims 23, 30, 31, and 64-66 are unpatentable under 35 U.S.C. §102(b) as being anticipated by Loeffler, U.S. Pat. No. 5,897,911 (Evidence App., Ex. C).

Whether claim 57 is unpatentable under 35 U.S.C. §103(a) as being unpatentable over Ragheb in view of Harish et al., U.S. Pat. No. 6,506,437 (Evidence App., Ex. D, hereinafter "Harish").

ARGUMENT

Rejection under 35 U.S.C. § 112, first paragraph

Claim 64

In the Final Office Action mailed 17 October 2007 (Evidence App., Ex. E, hereinafter "Final Office Action"), the examiner rejected claim 64 under §112, first paragraph, as failing to comply with the written description requirement. The examiner asserted that the amendment of claim 64 to include the limitation "temporarily placing a cover on the inner surface" is new matter. This limitation, according to the examiner, "implies a 'touching' relationship between the cover and the inner surface" and that "[t]his is new matter that is not supported by the specification as originally filed" (Final Office Action, p. 3) The examiner's assertion that this is new matter is incorrect.

Under the written description requirement, the specification must reasonably convey to those skilled in the art that the applicant was in possession of the claimed invention as of the date of invention. Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997). "To comply with the written description requirement of 35 U.S.C. §112, first paragraph, ... each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure." MPEP 2163(II)(A)(3)(b). The limitation in question, "temporarily placing a cover on the inner surface," is expressly supported in the originally filed disclosure, which states:

> Stent 10 can be temporarily mounted on a conventional mandrel such that the mandrel fits within hollow bore 22 and against inner surface 20 or first coating 28.

(Specification, page 16, lines 3-6 (Evidence App., Ex. F)). The passage that "the mandrel fits … against the inner surface" expressly supports the 'touching' relationship referred to by the examiner. Therefore, the rejection of claim 64 is deficient as a matter of law.

The Board is requested to reverse the rejection of claim 64 under §112, first paragraph.

Rejection under 35 U.S.C. § 102(e) over U.S. Pat. No. 6,299,604 (Ragheb et al.)

Claims 23, 32, 56, and 60

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), cert denied, 484 U.S. 827 (1987). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is **necessarily** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations and internal quotation marks omitted) (Appellants' emphasis).

Every element as set forth in independent claims 23 and 56 is not found, either expressly or inherently described, in Ragheb (Evidence App., Ex. A). Specifically, Ragheb does not disclose, expressly or inherently: (1) forming or applying on the inner surface of the stent a first coating having an angiogenic substance or substance facilitating angiogenesis, (2) forming or applying on the outer surface of the stent a second coating having a therapeutic substance capable of inhibiting migration or proliferation of smooth muscle cells, and (3) wherein the outer surface is free from the first coating and the inner surface is free from the second coating. Appellants pointed this out in their Amendment filed on 24 April 2007, to which the examiner responded by stating only that "one of skill in the art would know to place the angiogenic substance on the inner surface (where the blood is) and the antiproliferative on the outer surface (where the blood vessel cells are)" (Final Office Action, p. 5, first paragraph). This line of reasoning does not show (1) that mention of an angiogenic substance in Ragheb necessarily discloses placement of that angiogenic substance on the inner surface of the stent, (2) that mention of an antiproliferative substance in Ragheb necessarily discloses placement of that antiproliferative substance on the outer surface of the stent, and (3) that the mention of both substances necessarily discloses that the outer and inner surfaces are free from the angiogenic and antiproliferative substances, respectively. Therefore, the examiner's analysis is insufficient to establish a prima facie case of anticipation by Ragheb.

In stating that "one of skill in the art would know to place the angiogenic substance on the inner surface (where the blood is) and the antiproliferative on the outer surface (where the blood vessel cells are)," the examiner appears to propose new law: that the teaching of a reference can be combined with the knowledge of a person of ordinary skill in the art in determining anticipation under 35 U.S.C. §102. Any such proposal is contrary to well established patent law noted above. As previously quoted, In re Robertson provides that "[t]o establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill" (169 F.3d at 745, 49 USPQ2d at 1950-51). In that context, the term "recognized" refers to that which is inherently described, not something in addition thereto.

Even though Ragheb discusses a wide range of substances (col. 9, line 5 to col. 8, line 18) and discloses that some substances can be placed on different surfaces of a stent (e.g., col. 20, lines 15-18; col. 21, lines 41-67), Ragheb provides no disclosure as to the claimed mutually exclusive placement of the angiogenic and antiproliferative substances on different surfaces of the stent. The examiner has merely alleged the probability that a person of ordinary skill would know to make the claimed coating configuration. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 169 F.3d at 745, 49 USPQ2d at 1951 (citations and internal quotation marks omitted). Therefore, Ragheb does not describe the claimed invention to support a prima facie case of anticipation.

It has been held that a generic chemical formula or description, without more, could not anticipate a specific chemical formula or species because the generic disclosure encompassed a vast number of compounds or species. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962); In re Meyer, 599 F.2d 1026, 202 USPQ 175 (CCPA 1979). The disclosure of Ragheb is "generic" in the sense that it is silent as to a particular coating "species," namely the relative placement of angiogenic and antiproliferative substances. As such, Ragheb's long list of substances including mere mention of antiproliferative and angiogenic coating substances (e.g., col. 8, line 40; col. 9, lines 47 and 55; and col. 14, line 47) cannot anticipate the particular mutually exclusive placement of angiogenic and antiproliferative substances required in the claims. The fact remains, Ragheb does not disclose, expressly or inherently, the particular mutually exclusive placement of angiogenic and antiproliferative substances required in the claims.

Furthermore, the examiner's statement that "one of skill in the art would know to place the angiogenic substance on the inner surface (where the blood is) and the antiproliferative on the outer surface (where the blood vessel cells are)" is unsupported by evidence and is a purely hindsight evaluation based on Appellants' own disclosure (see Specification, Figures 5C and 5D, and page 19, line 9 through page 20, line 7). As best understood, the examiner appears to assert that angiogenic and antiproliferative substances are more desirable on certain stent surfaces. Ragheb suggests otherwise. In Ragheb, angiogenic and antiproliferative substances are described as being optionally present in layer 18 of Figure 1 (col. 9, line 47 and 55). Also, paclitaxel (an antiproliferative agent) is described as being optionally present in layer 18 (col. 14, line 47) or layer 16 (col. 15. lines 43-44) of Figure 11. As clearly shown in Figures 1 and 11 of Ragheb (reproduced below), layers 16 and 18 are located on both inner and outer surfaces of the structure 12. Significantly, angiogenic and antiproliferative substances are not mentioned where Ragheb discloses the possibility of having different therapeutic substance on different surfaces (col. 20, lines 15-18; col. 21, lines 41-67). Thus, Ragheb does not even suggest the particular mutually exclusive placement of angiogenic and antiproliferative substances required in the claims.

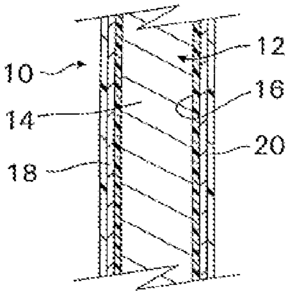


Fig. 1

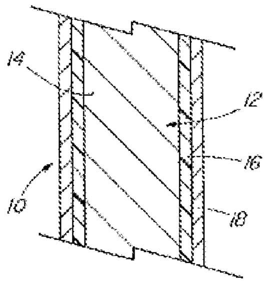


FIG. 11

Claims 32 and 60 depend from base claim 23 or 56 and, therefore, include every element of their respective base claim.

The Board is requested to reverse the rejection and order that claims 23, 32, 56, and 60 be passed to issue.

Rejection under 35 U.S.C. § 102(e) over U.S. Pat. No. 6,517,888 (Weber)

Claims 23, 45, 56, 58, and 59

Every element as set forth in claims 23 and 56 is not found, either expressly or inherently described, in Weber (Evidence App., Ex. B). Like Ragheb, Weber does not disclose, expressly or inherently: (1) forming or applying on the inner surface of the stent a first coating having an angiogenic substance or substance facilitating angiogenesis, (2) forming or applying on the outer surface of the stent a second coating having a therapeutic substance capable of inhibiting migration or proliferation of smooth muscle cells, and (3) wherein the outer surface is free from the first coating and the inner surface is free from the second coating. Appellants pointed this out in the Amendment filed on 24 April 2007, to which the examiner responded by stating only that "one of skill in the art would know to place the angiogenic substance on the inner surface (where the blood is) and the antiproliferative on the outer surface (where the blood vessel cells are)." (Final Office Action, p. 6, first paragraph). This line of reasoning fails to show (1) that mention of an angiogenic substance in Weber necessarily discloses placement of that angiogenic substance on the inner surface of the stent, (2) that the mention of an antiproliferative substance in Weber necessarily discloses placement of that antiproliferative substance on the outer surface of the stent, and (3) that mention of both these substances necessarily discloses that the outer and inner surfaces are free from the angiogenic and antiproliferative substances, respectively. Therefore, the examiner's analysis is insufficient to establish a prima facie case of anticipation by Weber.

Weber provides no disclosure as to the claimed mutually exclusive placement of angiogenic and antiproliferative substances on different surfaces of the stent. The examiner has merely alleged the probability that a person of ordinary skill would know to make the claimed coating configuration. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 169 F.3d at 745, 49 USPQ2d at 1950-51 (citations and internal quotation marks omitted). Clearly, Weber does not describe the claimed invention to support a prima facie case of anticipation.

The disclosure of Weber is "generic" in the sense that it is silent as to a particular coating "species," namely the relative placement of angiogenic and antiproliferative substances. Under In re Petering and In re Meyer, Weber's long list of substances including mere mention of antiproliferative and angiogenic substances (e.g., col. 6, line 41, and col. 7, line 18) cannot anticipate the particular mutually exclusive placement of angiogenic and antiproliferative substances required in the claims.

Appellants argued the point above during prosecution, stating that: "If each of the biological agent classes disclosed by Weber can independently be placed on either the outer surface or the inner surface of the stent, then Weber purportedly anticipates a vast number of stent coating permutations or species," and that such a finding of anticipation is impermissible under In re Petering (Amendment filed 24 April 2007, p.13, last paragraph). The examiner appears to have misconstrued this argument by asserting that "applicant has argued that each class of agents can be placed on the outer surface or inner surface" (Final Office Action, p. 6). In reality, Appellants argued that it is impermissible to read into Weber that every substance mentioned can be independently placed on one surface in combination with another substance placed on the opposite surface. The fact remains, Weber does not disclose, expressly or inherently, the particular mutually exclusive placement of angiogenic and antiproliferative substances required in the claims.

Claims 45, 58 and 59 depend from base claim 23 or 56 and, therefore, include every element of their respective base claim.

The Board is requested to reverse the rejection and order that claims 23, 45, 56, 58, and 59 be passed to issue.

Rejection under 35 U.S.C. § 102(e) over U.S. Pat. No. 5,897,911 (Loeffler)

Claim 23, 30 and 31

Every element as set forth in claim 23 is not found, either expressly or inherently described, in Loeffler (Evidence App., Ex. C). Like Ragheb and Weber, Loeffler does not disclose, expressly or inherently: (1) forming on the inner surface of the stent a first coating having an angiogenic substance (2) forming on the outer surface of the stent a second coating having a therapeutic substance capable of inhibiting migration or proliferation of smooth muscle cells, and (3) wherein the outer surface is free from the first coating and the inner surface is free from the second coating. Yet again, the examiner responded only by stating that “one of skill in the art would know to place the angiogenic substance on the inner surface (where the blood is) and the antiproliferative on the outer surface (where the blood vessel cells are)” (Office Action, p. 7, second paragraph). As already explained above, this line of reasoning is insufficient to establish a prima facie case of anticipation.

Loeffler provides no disclosure as to the claimed mutually exclusive placement of angiogenic and antiproliferative substances on different surfaces of the stent. The examiner has merely alleged the probability that a person of ordinary skill would make the claimed coating configuration, which is insufficient as a matter of law. See In re Robertson, 169 F.3d at 745, 49 USPQ2d at 1950-51.

The disclosure of Loeffler is “generic” in the sense that it is silent as to a particular coating “species,” namely the relative placement of angiogenic and antiproliferative substances. Under In re Petering and In re Meyer, Loeffler’s long list of substances (col. 2, line 56 through col. 3, line 32) including mere mention of antiproliferative and angiogenic substances in (col. 3, lines 16 and 21) cannot anticipate the particular mutually exclusive placement of angiogenic and antiproliferative substances required in the claims.

Appellants previously argued the above point as to Loeffler, which the examiner appears to have misconstrued by asserting that "applicant has argued that each class of agents can be placed on the outer surface or inner surface" (Final Office Action, p. 7). In reality, Appellants argued that it is impermissible to read into Loeffler that every substance mentioned can be independently placed on one surface in combination with another substance placed on an opposite surface. The fact remains, Loeffler does not disclose, expressly or inherently, the particular mutually exclusive placement of angiogenic and antiproliferative substances required in claim 23.

Claims 30 and 31 depend from claim 23 and, therefore, include every element of claim 23.

The Board is requested to reverse the rejection and order that claims 23, 30 and 31 be passed to issue.

Claim 64-66

Claim 64 requires "temporarily placing a cover on the inner surface of the stent." Claims 65 and 66 depend from claim 64 and, therefore, include all the elements of claim 64. This limitation of claims 64-66 is not found, either expressly or inherently described, in Loeffler. In Figures 1 and 2 of Loeffler (reproduced below), a stent 12 is positioned inside a mold 23 with a core pin 14 extending through the center of the stent. The core pin 14 is spaced apart from, not on, the inner surface of the stent. The gap between the core pin 14 and the inner surface of the stent 12 is evident from the cross-hatch lines representing stent struts or scaffolding that are located behind and spaced apart from the core pin.

FIG. 1

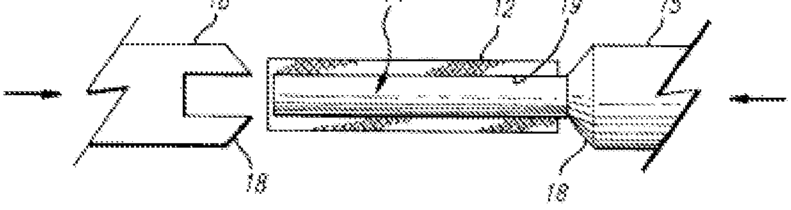
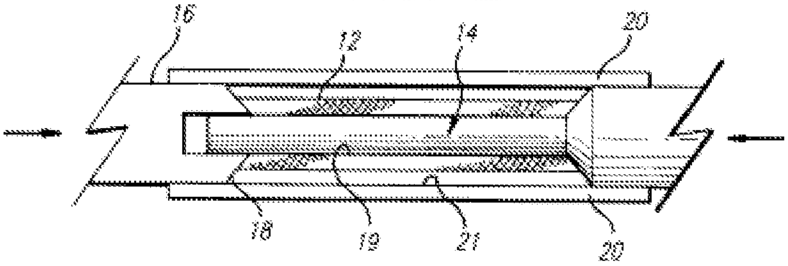
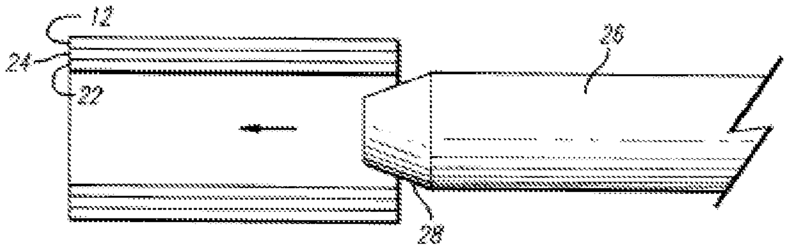


FIG. 2



The examiner erroneously asserts that Figure 3 of Loeffler (reproduced below) shows that the tapered mandrel 26 “fits snugly inside the stent 12” and, thereby, meets the limitation of claim 64. The examiner has overlooked the support tube 22 and polymer 24, which cause the mandrel 26 to be spaced apart from the stent inner surface. Figure 3 of Loeffler shows how a stent 12 can be encased in a polymer 24 by first applying the polymer 24 to the inner surface of the stent. A tapered mandrel 26 is subsequently inserted inside a support tube 22 beneath the polymer 24 to expand the polymer 24 snugly against the inner surface of the stent. Contrary to the examiner’s assertion, it is the polymer 24, not the mandrel 26, that is in contact with the stent inner surface. The tapered mandrel 26 is spaced apart from, not on, the inner surface of the stent by the polymer 24 and support tube 22. Therefore, Loeffler does not describe the claimed invention to support a prima facie case of anticipation.

FIG. 3



The Board is requested to reverse the rejection and order that claims 64-66 be passed to issue.

Rejection under 35 U.S.C. § 103(a) over U.S. Pat. No. 6,299,604 (Ragheb et al.) and U.S. Pat. No. 6,506,437 (Harish et al.)

Claim 57

The examiner rejected claim 57 under § 103(a) as being unpatentable over Ragheb in view of Harish (Evidence App., Ex. D). The examiner admits that Ragheb is silent as to the stent having cavities in the inner and outer surfaces (Final Office Action, p. 7). But the examiner argues that Harish discloses those elements and further that it would have been obvious to one having ordinary skill in the art to use the Harish stent having cavities in the coating method of Ragheb (id.).

Appellants do not dispute the examiner's characterization in the Final Office Action of that which Harish teaches. Appellants offer no opinion as to whether they agree or disagree with the examiner's contention that it would have been obvious to modify the coating method of Ragheb with the stent of Harish. However, claim 57 depends from claim 56 and, thereby, includes all the elements of claim 56. For the reasons discussed above in connection with claim 56, Ragheb fails to teach, suggest, or otherwise make obvious elements of claim 57, namely: (1) applying a first composition including a first therapeutic substance capable of facilitating angiogenesis on the inner surface of a stent, (2) applying second composition including a second therapeutic substance for inhibiting migration or proliferation of smooth muscle cells on the outer surface of the stent, and (3) wherein the outer surface is free from the first therapeutic substance and the inner surface is free from the second therapeutic substance. Harish offers nothing to cure this fatal flaw in the examiner's rejection and, therefore, the combination of Harish with Ragheb simply does not render the current invention obvious.

The Board is requested to reverse this rejection and order that claim 57 be passed to issue.

CONCLUSION

The examiner has failed, as a matter of law, to set forth a prima facie case for 35 U.S.C. §102 anticipation of claims 23, 32, 56, and 60 over Ragheb and, equally so, has failed as a matter of law to set forth a prima facie case for 35 U.S.C. § 103(a) obviousness of claim 57 over Ragheb in view of Harish. The examiner has also failed, as a matter of law, to set forth a case of anticipation under 35 U.S.C. § 102 of claims 23, 45, 56, 58, and 59 over Weber and of claims 23, 30, 31, and 64-60 over Loeffler. Appellants therefore respectfully request that the Board reverse the examiner's rejections *in toto* and order the application be passed to issue.

Date: March 3, 2008

Respectfully submitted,

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CLAIMS APPENDIX

The claims on appeal are:

23. A method of manufacturing a drug delivery coating for a stent, the stent including a tubular body having an outer surface and an inner surface, the method comprising:

forming a first coating on the inner surface of the stent, the first coating including an angiogenic substance and configured to release the angiogenic substance in the vessel; and

forming a second coating on the outer surface of the stent, the second coating including a therapeutic substance capable of inhibiting migration or proliferation of smooth muscle cells and configured to apply the therapeutic substance to the wall of the vessel,

wherein the outer surface is free from the first coating including the angiogenic substance and the inner surface is free from the second coating including the therapeutic substance.

30. The method of Claim 23, wherein forming the second coating comprises covering the inner surface of the stent prior to applying a composition containing the therapeutic substance to the stent.

31. The method of Claim 30, wherein the inner surface is covered by placing the stent on a mandrel.

32. The method of Claim 23, wherein the angiogenic substance is selected from the group consisting of vascular endothelial growth factor, fibroblast growth factors,

monocyte chemoattractant protein 1, transforming growth factor beta, transforming growth factor alpha, lipid factors, hypoxia-inducible factor 1-alpha, PR39, del 1, nicotine, insulin-like growth factors, placental growth factor, hepatocyte growth factor, estrogen, follistatin, proliferin, cytokines, tumor necrosis factor, erythropoietin, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, angiogenin, hormones, and genes that encode such substances.

45. The method of Claim 23, wherein the angiogenic substance is a hepatocyte growth factor.

56. A method of manufacturing a drug delivery coating for a stent, the stent including a tubular body having an outer surface and an inner surface, the method comprising:

applying a first composition to the inner surface of the stent, the first composition including a first therapeutic substance capable of facilitating angiogenesis; and

applying a second composition to the outer surface of the stent, the second composition including a second therapeutic substance, the second therapeutic substance capable of inhibiting migration or proliferation of smooth muscle cells,

wherein the first and second compositions are applied to the stent so that the outer surface is free from the first therapeutic substance and the inner surface is free from the second therapeutic substance.

57. The method of Claim 56, wherein the tubular body of the stent includes cavities in the inner and outer surfaces, and wherein the first and second compositions are applied to the stent to at least partially fill the cavities.

58. The method of Claim 56, wherein the first or second composition includes a polymer.

59. The method of Claim 56, wherein the first therapeutic substance is selected from the group consisting of vascular endothelial growth factor, fibroblast growth factors, monocyte chemoattractant protein 1, transforming growth factor beta, transforming growth factor alpha, lipid factors, hypoxia-inducible factor 1-alpha, PR39, del 1, nicotine, insulin-like growth factors, placental growth factor, hepatocyte growth factor, estrogen, follistatin, proliferin, cytokines, tumor necrosis factor, erythropoietin, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, angiogenin, hormones, and genes that encode such substances.

60. The method of Claim 56, wherein the second therapeutic substance is selected from the group consisting of actinomycin D, docetaxel and paclitaxel.

64. A method of manufacturing a coating for a stent, the stent including a tubular body having an outer surface and an inner surface, the method comprising:

temporarily placing a cover on the inner surface of the stent;

applying a first composition to the outer surface of the stent to form a first coating;

covering the first coating on the outer surface of the stent; and

applying a second composition to the inner surface of the stent to form a second coating.

65. The method of Claim 64, wherein the first composition includes a first therapeutic substance and the second composition includes a second therapeutic

substance.

66. The method of Claim 64, wherein the first composition includes a first polymeric material and the second composition includes a second polymeric material.

EVIDENCE APPENDIX

Attached hereto are the following exhibits.

A. U.S. Pat. No. 6,299,604 to Ragheb et al.

B. U.S. Patent No. 6,517,888 to Weber

C. U.S. Patent No. 5,897,911 to Loeffler

D. U.S. Patent No. 6,506,437 to Harish et al.

E. Final Office Action mailed October 17, 2007

F. Specification filed October 2, 2003 (copy of specification from parent application 09/846,498).

RELATED PROCEEDINGS APPENDIX

There are no related proceedings.

US006299604B1

(12) United States Patent
Ragheb et al.

(10) **Patent No.:** **US 6,299,604 B1**
(45) **Date of Patent:** **Oct. 9, 2001**

(54) **COATED IMPLANTABLE MEDICAL DEVICE**

(75) Inventors: **Anthony O. Ragheb**, West Lafayette; **Brian L. Bates**, Bloomington; **Neal E. Fearnot**, West Lafayette; **Thomas G. Kozma**, Lafayette; **William D. Voorhees, III**, West Lafayette, all of IN (US)

(73) Assignees: **Cook Incorporated**, Bloomington; **MED Institute Inc.**, West Lafayette, both of IN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/378,541**

(22) Filed: **Aug. 20, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/097,231, filed on Aug. 20, 1998.

(51) **Int. Cl.**^{7} **A61M 5/32**
(52) **U.S. Cl.** **604/265**; 623/1
(58) **Field of Search** 604/53, 265; 623/1, 623/11, 12; 424/423, 426; 514/772.2, 772.3, 822; 523/112, 113

(56) **References Cited**

U.S. PATENT DOCUMENTS

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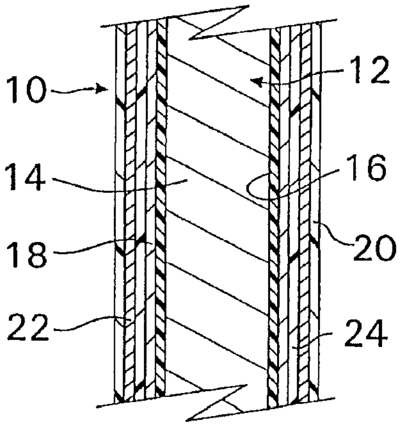
(57) ABSTRACT

A coated implantable medical device **10** includes a structure **12** adapted for introduction into the vascular system, esophagus, trachea, colon, biliary tract, or urinary tract; at least one coating layer **16** posited on one surface of the structure; and at least one layer **18** of a bioactive material posited on at least a portion of the coating layer **16**, wherein the coating layer **16** provides for the controlled release of the bioactive material from the coating layer. In addition, at least one porous layer **20** can be posited over the bioactive material layer **18**, wherein the porous layer is includes a polymer and provides for the controlled release of the bioactive material therethrough. Preferably, the structure **12** is a coronary stent. The porous layer **20** includes a polymer applied preferably by vapor or plasma deposition and provides for a controlled release of the bioactive material. It is particularly preferred that the polymer is a polyamide, parylene or a parylene derivative, which is deposited without solvents, heat or catalysts, and merely by condensation of a monomer vapor.

26 Claims, 5 Drawing Sheets



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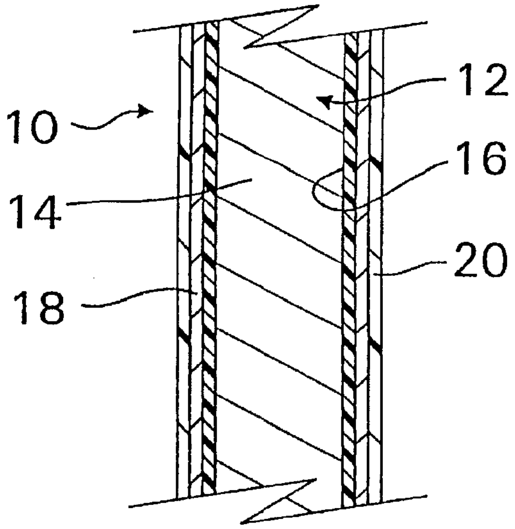

Fig. 1

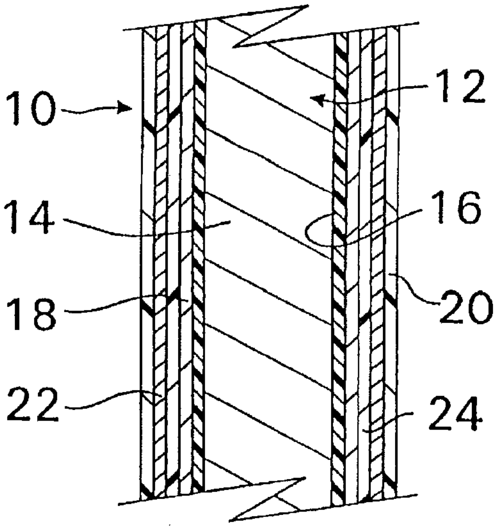

Fig. 2

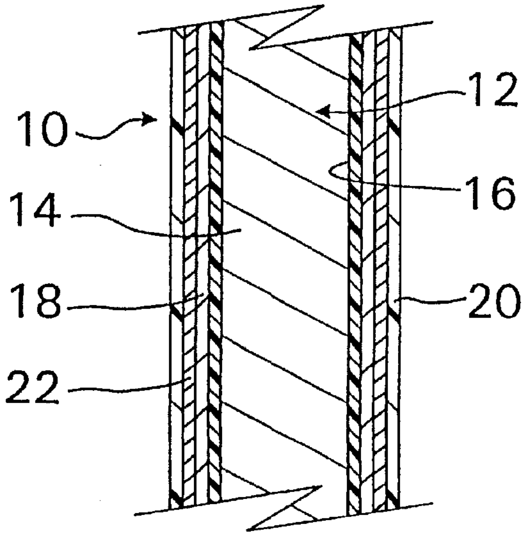

Fig. 3

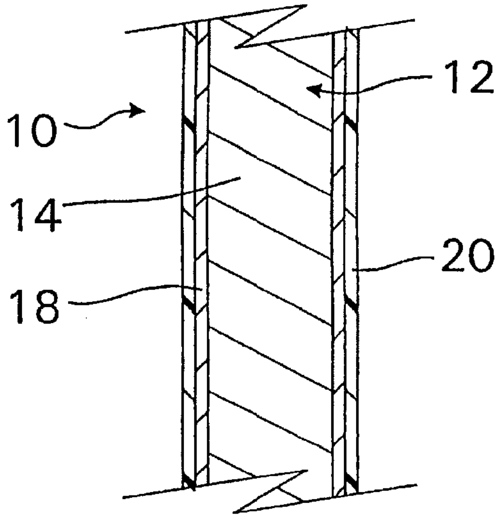

Fig.4

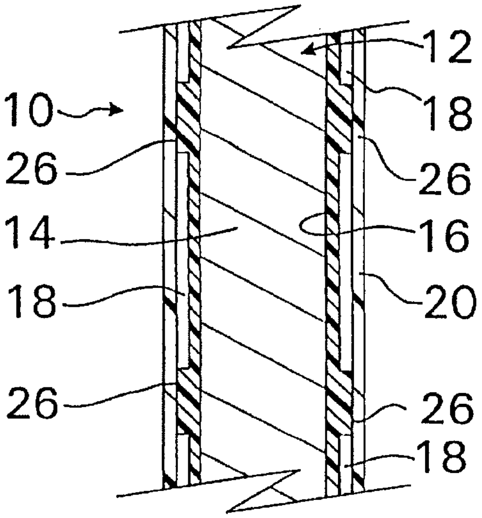

Fig.5

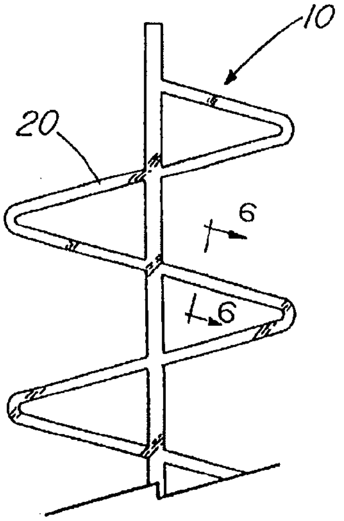

FIG. 7

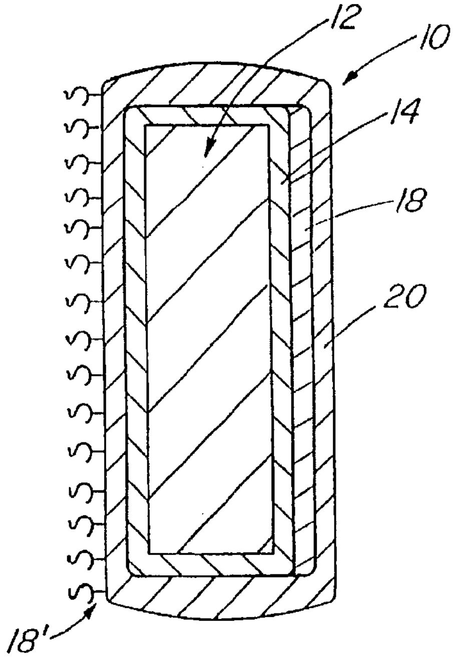

FIG. 6A

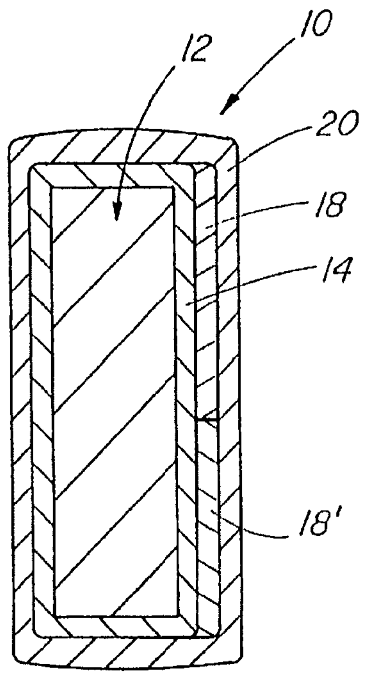

FIG. 6B

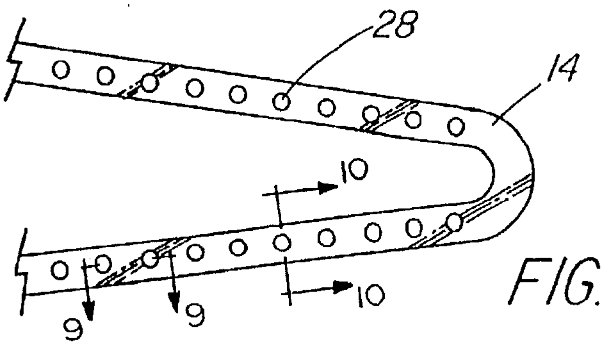

FIG. 8

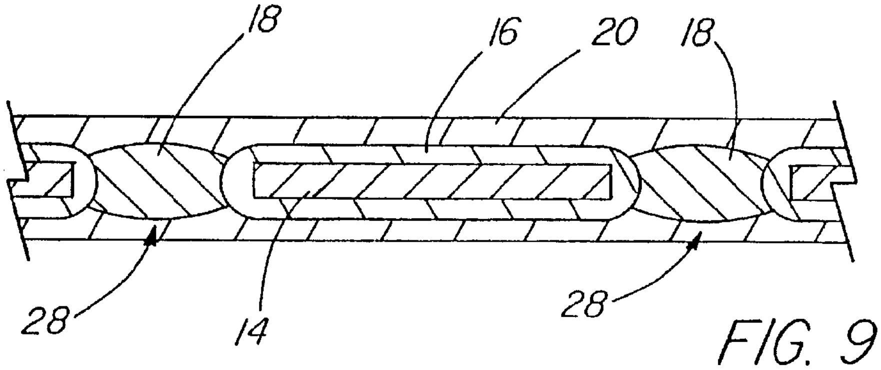

FIG. 9

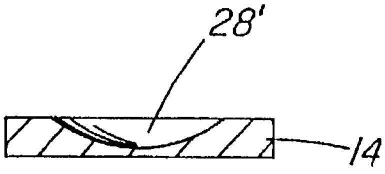

FIG. 10A

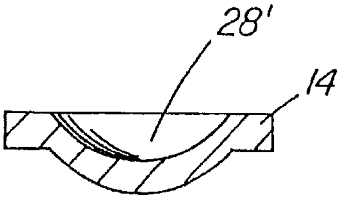

FIG. 10C

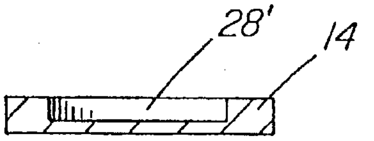

FIG. 10B

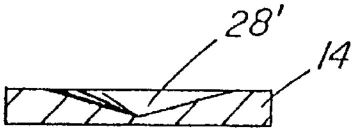

FIG. 10D

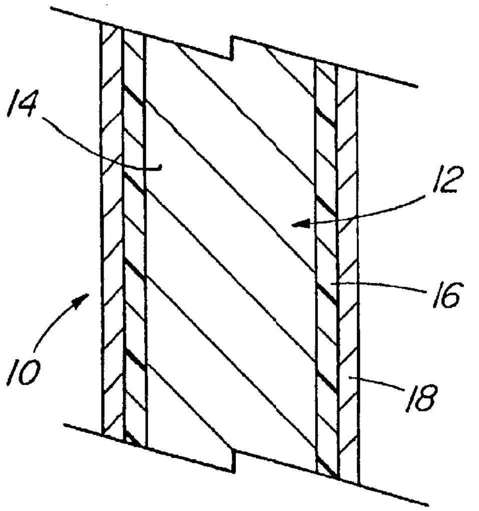

FIG. 11

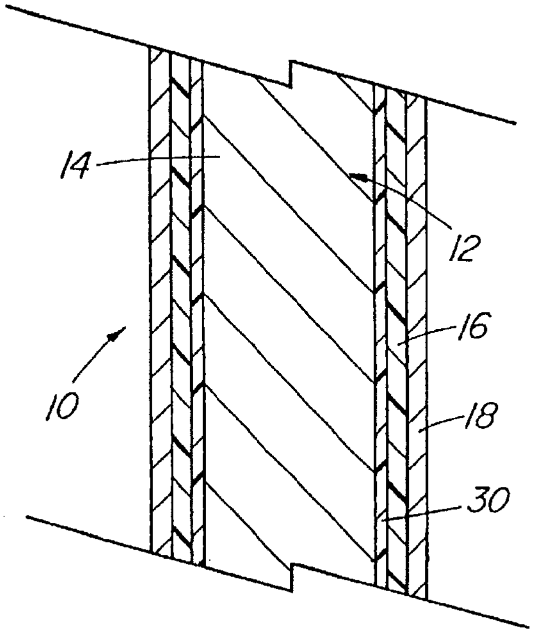

FIG. 12

COATED IMPLANTABLE MEDICAL DEVICE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to provisional application Ser. No. 60/097,231, filed Aug. 20, 1998.

TECHNICAL FIELD

This invention relates generally to human and veterinary medical devices, and more particularly to devices incorporating drugs or bioactive agents.

BACKGROUND OF THE INVENTION

It has become common to treat a variety of medical conditions by introducing an implantable medical device partly or completely into the esophagus, trachea, colon, biliary tract, urinary tract, vascular system or other location within a human or veterinary patient. For example, many treatments of the vascular system entail the introduction of a device such as a stent, a catheter, a balloon, a wire guide, a cannula, or the like. However, when such a device is introduced into and manipulated through the vascular system, the blood vessel walls can be disturbed or injured. Clot formation or thrombosis often results at the injured site, causing stenosis or occlusion of the blood vessel. Moreover, if the medical device is left within the patient for an extended period of time, thrombus often forms on the device itself, again causing stenosis or occlusion. As a result, the patient is placed at risk of a variety of complications, including heart attack, pulmonary embolism, and stroke. Thus, the use of such a medical device can entail the risk of precisely the problems that its use was intended to ameliorate.

Another way in which blood vessels undergo stenosis is through disease. Probably the most common disease causing stenosis of blood vessels is atherosclerosis. Atherosclerosis is a condition which commonly affects the coronary arteries, the aorta, the iliofemoral arteries and the carotid arteries. Atherosclerotic plaques of lipids, fibroblasts, and fibrin proliferate and cause obstruction of an artery or arteries. As the obstruction increases, a critical level of stenosis is reached, to the point where the flow of blood past the obstruction is insufficient to meet the metabolic needs of the tissue distal to (downstream of) the obstruction. The result is ischemia.

Many medical devices and therapeutic methods are known for the treatment of atherosclerotic disease. One particularly useful therapy for certain atherosclerotic lesions is percutaneous transluminal angioplasty (PTA). During PTA, a balloon-tipped catheter is inserted in a patient's artery, the balloon being deflated. The tip of the catheter is advanced to the site of the atherosclerotic plaque to be dilated. The balloon is placed within or across the stenotic segment of the artery, and then inflated. Inflation of the balloon "cracks" the atherosclerotic plaque and expands the vessel, thereby relieving the stenosis, at least in part.

While PTA presently enjoys wide use, it suffers from two major problems. First, the blood vessel may suffer acute occlusion immediately after or within the initial hours after the dilation procedure. Such occlusion is referred to as "abrupt closure." Abrupt closure occurs in perhaps five percent or so of the cases in which PTA is employed, and can result in myocardial infarction and death if blood flow is not restored promptly. The primary mechanisms of abrupt closures are believed to be elastic recoil, arterial dissection and/or thrombosis. It has been postulated that the delivery of an appropriate agent (such as an antithrombic) directly into the arterial wall at the time of angioplasty could reduce the incidence of thrombotic acute closure, but the results of attempts to do so have been mixed.

A second major problem encountered in PTA is the re-narrowing of an artery after an initially successful angioplasty. This re-narrowing is referred to as "restenosis" and typically occurs within the first six months after angioplasty. Restenosis is believed to arise through the proliferation and migration of cellular components from the arterial wall, as well as through geometric changes in the arterial wall referred to as "remodeling." It has similarly been postulated that the delivery of appropriate agents directly into the arterial wall could interrupt the cellular and/or remodeling events leading to restenosis. However, like the attempts to prevent thrombotic acute closure, the results of attempts to prevent restenosis in this manner have been mixed.

Non-atherosclerotic vascular stenosis may also be treated by PTA. For example, Takayasu arteritis or neurofibromatosis may cause stenosis by fibrotic thickening of the arterial wall. Restenosis of these lesions occurs at a high rate following angioplasty, however, due to the fibrotic nature of the diseases. Medical therapies to treat or obviate them have been similarly disappointing.

A device such as an intravascular stent can be a useful adjunct to PTA, particularly in the case of either acute or threatened closure after angioplasty. The stent is placed in the dilated segment of the artery to mechanically prevent abrupt closure and restenosis. Unfortunately, even when the implantation of the stent is accompanied by aggressive and precise antiplatelet and anticoagulation therapy (typically by systemic administration), the incidence of thrombotic vessel closure or other thrombotic complication remains significant, and the prevention of restenosis is not as successful as desired. Furthermore, an undesirable side effect of the systemic antiplatelet and anticoagulation therapy is an increased incidence of bleeding complications, most often at the percutaneous entry site.

Other conditions and diseases are treatable with stents, catheters, cannulae and other devices inserted into the esophagus, trachea, colon, biliary tract, urinary tract and other locations in the body, or with orthopedic devices, implants, or replacements. It would be desirable to develop devices and methods for reliably delivering suitable agents, drugs or bioactive materials directly into a body portion during or following a medical procedure, so as to treat or prevent such conditions and diseases, for example, to prevent abrupt closure and/or restenosis of a body portion such as a passage, lumen or blood vessel. As a particular example, it would be desirable to have devices and methods which can deliver an antithrombic or other medication to the region of a blood vessel which has been treated by PTA, or by another interventional technique such as atherectomy, laser ablation, or the like. It would also be desirable that such devices would deliver their agents over both the short term (that is, the initial hours and days after treatment) and the long term (the weeks and months after treatment). It would also be desirable to provide precise control over the delivery rate for the agents, drugs or bioactive materials, and to limit systemic exposure to them. This would be particularly advantageous in therapies involving the delivery of a chemotherapeutic agent to a particular organ or site through an intravenous catheter (which itself has the advantage of reducing the amount of agent needed for successful treatment), by preventing stenosis both along the catheter and at the catheter tip. A wide variety of other therapies could be similarly improved. Of course, it would also be desirable to avoid degradation of the agent, drug or bioactive material during its incorporation on or into any such device.

SUMMARY OF THE INVENTION

The foregoing problems are solved and a technical advance is achieved in an illustrative vascular stent or other implantable medical device that provides a controlled release of an agent, drug or bioactive material into the vascular or other system, or other location in the body, in which a stent or other device is positioned. Applicants have discovered that the degradation of the agent, a drug or a bioactive material that is applied to such a device can be avoided by positing a coating layer on one surface of the device structure. The agent, drug or bioactive material is posited over at least a portion of the coating layer, wherein the coating layer provides for a controlled release of the bioactive material posited thereon. Furthermore, the medical device further includes a porous layer posited over the bioactive material wherein the porous layer is composed of a polymer and the polymer provides for a controlled release of the bioactive material through the porous layer.

In one aspect, the coating layer comprises a non-porous material of for example a parylene derivative. This coating layer has a thickness preferably in a range from 50 to 500,000 Angstroms (Å), more preferably in a range from 100,000 to 500,000 Å, and illustratively approximately 200,000 Å, In another aspect, the non-porous material is either an adsorbent or an absorbent material, where the coating layer of the adsorbent material has a thickness of approximately 230,000 Å.

In another aspect of the invention, the bioactive material layer includes a chimeric monoclonal antibody such as an antiplatelet GP IIb/IIIa antibody.

In still another aspect of the invention, an adhesive promotion layer is posited on one surface of the structure on which the coating layer is posited over at least a portion thereof. Preferably the adhesion promotion layer includes silane having a thickness in range of 0.5 to 5,000 Å.

Applicants have also discovered that the degradation of an agent, a drug or a bioactive material applied to such a device may be avoided by covering the agent, drug or bioactive material with a porous layer of a biocompatible polymer that is applied without the use of solvents, catalysts, heat or other chemicals or techniques, which would otherwise be likely to degrade or damage the agent, drug or material. Those biocompatible polymers may be applied preferably by vapor deposition or plasma deposition, and may polymerize and cure merely upon condensation from the vapor phase, or may be photolytically polymerizable and are expected to be useful for this purpose. However, it should be recognized that other coating techniques may also be employed.

Preferably, when the device is intended for use in the vascular system, the bioactive material in the at least one layer is heparin or another antiplatelet or antithrombotic agent, or dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, or another dexamethasone derivative or anti-inflammatory steroid. Furthermore, a wide range of other bioactive materials can be employed, including, but not limited to, the following categories of agents: thrombolytics, vasodilators, antihypertensive agents, antimicrobials or antibiotics, antimitotics, antiproliferatives, antisecretory agents, non-steroidal anti-inflammatory drugs, immunosuppressive agents, growth factors and growth factor antagonists, antitumor and/or chemotherapeutic agents, antipolymerases, antiviral agents, photodynamic therapy agents, antibody targeted therapy agents, prodrugs, sex hormones, free radical scavengers, antioxidants, biologic agents, radiotherapeutic agents, radiopaque agents and radiolabelled agents. The major restriction is that the bioactive material must be able to withstand the coating techniques, for example, the vacuum employed during vapor deposition or plasma deposition of the at least one porous layer. In other words, the bioactive material must have a relatively low vapor pressure at the deposition temperature, typically, near or at room temperature.

The at least one porous layer is preferably composed of a polyamide, parylene or a parylene derivative applied by catalyst-free vapor deposition and is conveniently about 5,000 to 250,000 Å thick, which is adequate to provide a controlled release of the bioactive material. "Parylene" is both a generic name for a known group of polymers based on p-xylylene and made by vapor phase polymerization, and a name for the unsubstituted form of the polymer; the latter usage is employed herein. More particularly, parylene or a parylene derivative is created by first heating p-xylene or a suitable derivative at an appropriate temperature (for example, at about 950° C.) to produce the cyclic dimer di-p-xylylene (or a derivative thereof). The resultant solid can be separated in pure form, and then cracked and pyrolyzed at an appropriate temperature (for example, at about 680° C.) to produce a monomer vapor of p-xylylene (or derivative); the monomer vapor is cooled to a suitable temperature (for example, below 50° C.) and allowed to condense on the desired object, for example, on the at least one layer of bioactive material. The resultant polymer has the repeating structure $-(CH_2C_6H_4CH_2)_n-$, with n equal to about 5,000, and a molecular weight in the range of 500,000.

As indicated, parylene and parylene derivative coatings applicable by vapor deposition are known for a variety of biomedical uses, and are commercially available from or through a variety of sources, including Specialty Coating Systems (100 Deposition Drive, Clear Lake, Wis. 54005), Para Tech Coating, Inc. (35 Argonaut, Aliso Viejo, Calif. 92656) and Advanced Surface Technology, Inc. (9 Linnel Circle, Billerica, Mass. 01821-3902).

The at least one porous layer can alternatively be applied by plasma deposition. Plasma is an ionized gas maintained under vacuum and excited by electrical energy, typically in the radiofrequency range. Because the gas is maintained under vacuum, the plasma deposition process occurs at or near room temperature. Plasma can be used to deposit polymers such as poly(ethylene oxide), poly(ethylene glycol), and poly(propylene oxide), as well as polymers of silicone, methane, tetrafluoroethylene (including TEFLON brand polymers), tetramethyldisiloxane, and others.

While the foregoing represents some preferred embodiments of the present invention, other polymer systems may also be employed, e.g., polymers derived from photopolymerizeable monomers. Also, other coating techniques may be utilized, e.g., dipping, spraying, and the like.

The device may include two or more layers of different bioactive materials atop the structure. However, for the purposes of the present invention, the same bioactive material will generally not be posited on the different surfaces of the device within the same layer. In other words, each surface of the device structure will carry a different bioactive material or materials except where the bioactive material is the innermost or outermost layer, e.g. heparin may form the innermost layer or the outermost layer or both. These additional layers may be placed directly atop one another or can be separated by additional porous polymer layers between each of them. Additionally, the layers of bioactive materials can comprise a mixture of different bioactive materials. The porous layers are also preferably composed of parylene or a parylene derivative. Advantageously, the two or more bioactive materials can have different solubilities, and the layer containing the less soluble bioactive material (for example, dexamethasone) is preferably posited above the layer containing the more soluble bioactive material (for example, heparin). Unexpectedly, this has been found to increase the in vitro release rate of some relatively less soluble materials such as dexamethasone, while simultaneously decreasing the release rate of some relatively more soluble materials such as heparin.

While the structure included in the device may be configured in a variety of ways, the structure is preferably configured as a vascular stent composed of a biocompatible metal such as stainless steel, nickel, silver, platinum, gold, titanium, tantalum, iridium, tungsten, Nitinol, inconel, or the like. An additional substantially nonporous coating layer of parylene or a parylene derivative or other biocompatible polymer of about 50,000 to 500,000 Å thick may be posited directly atop the vascular stent, beneath the at least one layer of bioactive material. The additional coating layer can merely be relatively less porous than the at least one porous layer, but preferably is substantially nonporous, that is, sufficiently nonporous to render the stent essentially impervious to blood during normal circumstances of use.

The device and methods of the present invention are useful in a wide variety of locations within a human or veterinary patient, such as in the esophagus, trachea, colon, biliary tract, urinary tract and vascular system, as well as for subdural and orthopedic devices, implants or replacements. They are particularly advantageous for reliably delivering suitable bioactive materials during or following an intravascular procedure, and find particular use in preventing abrupt closure and/or restenosis of a blood vessel. More particularly, they permit, for example, the delivery of an antithrombotic, an antiplatelet, an anti-inflammatory steroid, or another medication to the region of a blood vessel which has been opened by PTA. Likewise, it allows for the delivery of one bioactive material to, for example, the lumen of a blood vessel and another bioactive material to the vessel wall. The use of a porous polymer layer permits the release rate of a bioactive material to be carefully controlled over both the short and long terms.

These and other aspects of the present invention will be appreciated by those skilled in the art upon the reading and understanding of the specification.

In another aspect of the invention, the bioactive material is attached to the non-porous layer and is advantageously eluted for prolonged periods of time. The non-porous layer is attached to the base material of the structure. The non-porous layer can be any of those previously or subsequently listed herein, and, likewise, the bioactive material can be any of those previously or subsequently listed herein. Conveniently, and in a preferred embodiment, a glycoprotein IIb/IIIa inhibitor such as commercially available ReoPro™ is attached to a non-porous layer of parylene positioned on the outer surface of the medical device such as a coronary stent. The ReoPro™ is advantageously eluted from the surface of the stent for prolonged periods of time.

BRIEF DESCRIPTION OF THE DRAWING

A better understanding of the present invention will now be had upon reference to the following detailed description, when read in conjunction with the accompanying drawing, wherein like reference characters refer to like parts throughout the several views, and in which:

FIG. **1** is a cross-sectional view of a first preferred embodiment of the present invention;

FIG. **2** is a cross-sectional view of another preferred embodiment of the present invention;

FIG. **3** is a cross-sectional view of yet another preferred embodiment of the present invention;

FIG. **4** is a cross-sectional view of a further preferred embodiment of the present invention;

FIG. **5** is a cross-sectional view of an additional preferred embodiment of the present invention;

FIGS. **6A** and **6B** are cross-sectional views of an additional preferred embodiment of the present invention;

FIG. **7** is a cross-sectional view of an additional preferred embodiment of the present invention;

FIG. **8** is a partial, enlarged top view of FIG. **7**;

FIG. **9** is an enlarged, sectional view along lines **9**—**9** of FIG. **8**;

FIGS. **10A**–**10D** are enlarged cross-sectional views along lines **10**—**10** of FIG. **8**;

FIG. **11** depicts another aspect of the medical device of FIG. **1** utilizing a polymer coating layer with a bioactive material attached thereto; and

FIG. **12** depicts still another aspect of the medical device of FIG. **11** in which the polymer coating layer is adhered to the outer surface of the device base material using an adhesive promotion layer.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

With reference now to FIG. **1**, an implantable medical device **10** in accordance with the present invention is shown and first comprises a structure **12** adapted for introduction into a human or veterinary patient. "Adapted" means that the structure **12** is shaped and sized for such introduction. For clarity, only a portion of the structure **12** is shown in FIG. **1**.

By way of example, the structure **12** is configured as a vascular stent particularly adapted for insertion into the vascular system of the patient. However, this stent structure can be used in other systems and sites such as the esophagus, trachea, colon, biliary ducts, urethra and ureters, subdural among others. Indeed, the structure **12** can alternatively be configured as any conventional vascular or other medical device, and can include any of a variety of conventional stents or other adjuncts, such as helical wound strands, perforated cylinders, or the like. Moreover, because the problems addressed by the present invention arise with respect to those portions of the device actually positioned within the patient, the inserted structure **12** need not be an entire device, but can merely be that portion of a vascular or other device which is intended to be introduced into the patient. Accordingly, the structure **12** can be configured as at least one of, or any portion of, a catheter, a wire guide, a cannula, a stent, a vascular or other graft, a cardiac pacemaker lead or lead tip, a cardiac defibrillator lead or lead tip, a heart valve, or an orthopedic device, appliance, implant, or replacement. The structure **12** can also be configured as a combination of portions of any of these.

Most preferably, however, the structure **12** is configured as a vascular stent such as the commercially available Gianturco-Roubin FLEX-STENT® or GR II™ coronary stent from Cook Incorporated, Bloomington, Ind. Such stents are typically about 10 to about 60 mm in length and designed to expand to a diameter of about 2 to about 6 mm when inserted into the vascular system of the patient. The Gianturco-Roubin stent in particular is typically about 12 to about 25 mm in length and designed to expand to a diameter of about 2 to about 4 mm when so inserted.

These stent dimensions are, of course, applicable to exemplary stents employed in the coronary arteries. Structures such as stents or catheter portions intended to be employed at other sites in the patient, such as in the aorta, esophagus, trachea, colon, biliary tract, or urinary tract will have different dimensions more suited to such use. For example, aortic, esophageal, tracheal and colonic stents may have diameters up to about 25 mm and lengths about 100 mm or longer.

The structure **12** is composed of a base material **14** suitable for the intended use of the structure **12**. The base material **14** is preferably biocompatible, although cytotoxic or other poisonous base materials may be employed if they are adequately isolated from the patient. Such incompatible materials may be useful in, for example, radiation treatments in which a radioactive material is positioned by catheter in or close to the specific tissues to be treated. Under most circumstances, however, the base material **14** of the structure **12** should be biocompatible.

A variety of conventional materials can be employed as the base material **14**. Some materials may be more useful for structures other than the coronary stent exemplifying the structure **12**. The base material **14** may be either elastic or inelastic, depending upon the flexibility or elasticity of the polymer layers to be applied over it. The base material may be either biodegradable or non-biodegradable, and a variety of biodegradable polymers are known. Moreover, some biologic agents have sufficient strength to serve as the base material **14** of some useful structures **12**, even if not especially useful in the exemplary coronary stent.

Accordingly, the base material **14** can include at least one of stainless steel, tantalum, titanium, nitinol, gold, platinum, inconel, iridium, silver, tungsten, or another biocompatible metal, or alloys of any of these; carbon or carbon fiber; cellulose acetate, cellulose nitrate, silicone, polyethylene teraphthalate, polyurethane, polyamide, polyester, polyorthoester, polyanhydride, polyether sulfone, polycarbonate, polypropylene, high molecular weight polyethylene, polytetrafluoroethylene, or another biocompatible polymeric material, or mixtures or copolymers of these; polylactic acid, polyglycolic acid or copolymers thereof, a polyanhydride, polycaprolactone, polyhydroxybutyrate valerate or another biodegradable polymer, or mixtures or copolymers of these; a protein, an extracellular matrix component, collagen, fibrin or another biologic agent; or a suitable mixture of any of these. Stainless steel is particularly useful as the base material **14** when the structure **12** is configured as a vascular stent.

Of course, when the structure **12** is composed of a radiolucent material such as polypropylene, polyethylene, or others above, a conventional radiopaque coating may and preferably should be applied to it. The radiopaque coating provides a means for identifying the location of the structure **12** by X-ray or fluoroscopy during or after its introduction into the patient's vascular system.

With continued reference to FIG. **1**, the vascular device **10** of the present invention next comprises at least one layer **18** of a bioactive material posited on one surface of the structure **12**. For the purposes of the present invention, at least one bioactive material is posited on one surface of the structure **12**, and the other surface will either contain no bioactive material or one or more different bioactive materials. In this manner, one or more bioactive materials or drugs may be delivered, for example, with a vascular stent, to the blood stream from the lumen surface of the stent, and a different treatment may be delivered on the vessel surface of the stent. A vast range of drugs, medicaments and materials may be employed as the bioactive material in the layer **18**, so long as the selected material can survive exposure to the vacuum drawn during vapor deposition or plasma deposition. Particularly useful in the practice of the present invention are materials which prevent or ameliorate abrupt closure and restenosis of blood vessels previously opened by stenting surgery or other procedures. Thrombolytics (which dissolve, break up or disperse thrombi) and antithrombogenics (which interfere with or prevent the formation of thrombi) are especially useful bioactive materials when the structure **12** is a vascular stent. Particularly preferred thrombolytics are urokinase, streptokinase, and the tissue plasminogen activators. Particularly preferred antithrombogenics are heparin, hirudin, and the antiplatelets.

Urokinase is a plasminogen activating enzyme typically obtained from human kidney cell cultures. Urokinase catalyzes the conversion of plasminogen into the fibrinolytic plasmin, which breaks down fibrin thrombi.

Heparin is a mucopolysaccharide anticoagulant typically obtained from porcine intestinal mucosa or bovine lung. Heparin acts as a thrombin inhibitor by greatly enhancing the effects of the blood's endogenous antithrombin III. Thrombin, a potent enzyme in the coagulation cascade, is key in catalyzing the formation of fibrin. Therefore, by inhibiting thrombin, heparin inhibits the formation of fibrin thrombi. Alternatively, heparin may be covalently bound to the outer layer of structure **12**. Thus, heparin would form the outermost layer of structure **12** and would not be readily degraded enzymatically, and would remain active as a thrombin inhibitor.

Of course, bioactive materials having other functions can also be successfully delivered by the device **10** of the present invention. For example, an antiproliferative agent such as methotrexate will inhibit over-proliferation of smooth muscle cells and thus inhibit restenosis of the dilated segment of the blood vessel. The antiproliferative is desirably supplied for this purpose over a period of about four to six months. Additionally, localized delivery of an antiproliferative agent is also useful for the treatment of a variety of malignant conditions characterized by highly vascular growth. In such cases, the device **10** of the present invention could be placed in the arterial supply of the tumor to provide a means of delivering a relatively high dose of the antiproliferative agent directly to the tumor.

A vasodilator such as a calcium channel blocker or a nitrate will suppress vasospasm, which is common following angioplasty procedures. Vasospasm occurs as a response to injury of a blood vessel, and the tendency toward vasospasm decreases as the vessel heals. Accordingly, the vasodilator is desirably supplied over a period of about two to three weeks. Of course, trauma from angioplasty is not the only vessel injury which can cause vasospasm, and the device **10** may be introduced into vessels other than the coronary arteries, such as the aorta, carotid arteries, renal arteries, iliac arteries or peripheral arteries for the prevention of vasospasm in them.

A variety of other bioactive materials are particularly suitable for use when the structure **12** is configured as something other than a coronary stent. For example, an anti-cancer chemotherapeutic agent can be delivered by the device **10** to a localized tumor. More particularly, the device **10** can be placed in an artery supplying blood to the tumor or elsewhere to deliver a relatively high and prolonged dose of the agent directly to the tumor, while limiting systemic exposure and toxicity. The agent may be a curative, a pre-operative debulker reducing the size of the tumor, or a palliative which eases the symptoms of the disease. It should be noted that the bioactive material in the present invention is delivered across the device **10**, and not by passage from an outside source through any lumen defined in the device **10**, such as through a catheter employed for conventional chemotherapy. The bioactive material of the present invention may, of course, be released from the device **10** into any lumen defined in the device, or to tissue in contact with the device and that the lumen may carry some other agent to be delivered through it. For example, tamoxifen citrate, Taxol® or derivatives thereof Proscar®, Hytrin®, or Eulexin® may be applied to the tissue-exposed surface of the device for delivery to a tumor located, for example in breast tissue or the prostate.

Dopamine or a dopamine agonist such as bromocriptine mesylate or pergolide mesylate is useful for the treatment of neurological disorders such as Parkinson's disease. The device **10** could be placed in the vascular supply of the thalamic substantia nigra for this purpose, or elsewhere, localizing treatment in the thalamus.

A wide range of other bioactive materials can be delivered by the device **10**. Accordingly, it is preferred that the bioactive material contained in the layer **18** includes at least one of heparin, covalent heparin, or another thrombin inhibitor, hirudin, hirulog, argatroban, D-phenylalanyl-L-poly-L-arginyl chloromethyl ketone, or another antithrombogenic agent, or mixtures thereof; urokinase, streptokinase, a tissue plasminogen activator, or another thrombolytic agent, or mixtures thereof; a fibrinolytic agent; a vasospasm inhibitor; a calcium channel blocker, a nitrate, nitric oxide, a nitric oxide promoter or another vasodilator; Hytrin® or other antihypertensive agents; an antimicrobial agent or antibiotic; aspirin, ticlopidine, a glycoprotein IIb/IIIa inhibitor or another inhibitor of surface glycoprotein receptors, or another antiplatelet agent; colchicine or another antimitotic, or another microtubule inhibitor, dimethyl sulfoxide (DMSO), a retinoid or another antisecretory agent; cytochalasin or another actin inhibitor; or a remodelling inhibitor; deoxyribonucleic acid, an antisense nucleotide or another agent for molecular genetic intervention; methotrexate or another antimetabolite or antiproliferative agent; tamoxifen citrate, Taxol® or the derivatives thereof, or other anti-cancer chemotherapeutic agents; dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate or another dexamethasone derivative, or another anti-inflammatory steroid or non-steroidal antiinflammatory agent; cyclosporin or another immunosuppressive agent; trapidal (a PDGF antagonist), angiopeptin (a growth hormone antagonist), angiogenin, a growth factor or an anti-growth factor antibody, or another growth factor antagonist; dopamine, bromocriptine mesylate, pergolide mesylate or another dopamine agonist; ^{60}Co (5.3 year half life), ^{192}Ir (73.8 days), ^{32}P (14.3 days), ^{111}In (68 hours), ^{90}Y (64 hours), ^{99m}Tc (6 hours) or another radiotherapeutic agent; iodine-containing compounds, barium-containing compounds, gold, tantalum, platinum, tungsten or another heavy metal functioning as a radiopaque agent; a peptide, a protein, an enzyme, an extracellular matrix component, a cellular component or another biologic agent; captopril, enalapril or another angiotensin converting enzyme (ACE) inhibitor; ascorbic acid, alpha tocopherol, superoxide dismutase, deferoxamine, a 21-aminosteroid (lasaroid) or another free radical scavenger, iron chelator or antioxidant; a ^{14}C-, ^{3}H-, ^{131}I-, ^{32}P- or ^{36}S-radiolabelled form or other radiolabelled form of any of the foregoing; estrogen or another sex hormone; AZT or other antipolymerases; acyclovir, famciclovir, rimantadine hydrochloride, ganciclovir sodium, Norvir, Crixivan, or other antiviral agents; 5-aminolevulinic acid, meta-tetrahydroxyphenylchlorin, hexadecafluoro zinc phthalocyanine, tetramethyl hematoporphyrin, rhodamine 123 or other photodynamic therapy agents; an IgG2 Kappa antibody against Pseudomonas aeruginosa exotoxin A and reactive with A431 epidermoid carcinoma cells, monoclonal antibody against the noradrenergic enzyme dopamine beta-hydroxylase conjugated to saporin or other antibody targeted therapy agents; gene therapy agents; and enalapril and other prodrugs; Proscar®, Hytrin® or other agents for treating benign prostatic hyperplasia (BHP) or a mixture of any of these; and various forms of small intestine submucosa (SIS).

In a particularly preferred aspect, the layer of bioactive material contains preferably from about 0.01 mg to about 10 mg and more preferably from about 0.1 mg to about 4 mg of the bioactive material per cm^2 of the gross surface area of the structure. "Gross surface area" refers to the area calculated from the gross or overall extent of the structure, and not necessarily to the actual surface area of the particular shape or individual parts of the structure. In other terms, about 100 μg to about 300 μg of drug per 0.001 inch of coating thickness may be contained on the device surface.

When the structure **12** is configured as a vascular stent, however, particularly preferred materials for the bioactive material of the layer **18** are heparin, anti-inflammatory steroids including but not limited to dexamethasone and its derivatives, and mixtures of heparin and such steroids.

Still with reference to FIG. **1**, the device **10** of the present invention also comprises at least one porous layer **20** posited over the layer **18** of bioactive material and the bioactive-material-free surface. The purpose of the porous layer **20** is to provide a controlled release of the bioactive material when the device **10** is positioned in the vascular system of a patient. The thickness of the porous layer **20** is chosen so as to provide such control.

More particularly, the porous layer **20** is composed of a polymer deposited on the bioactive material layer **18**, preferably by vapor deposition. Plasma deposition may also be useful for this purpose. Preferably, the layer **20** is one that is polymerized from a vapor which is free of any solvent, catalysts or similar polymerization promoters. Also preferably, the polymer in the porous layer **20** is one which automatically polymerizes upon condensation from the vapor phase, without the action of any curative agent or activity such as heating, the application of visible or ultraviolet light, radiation, ultrasound, or the like. Most preferably, the polymer in the porous layer **20** is polyimide, parylene or a parylene derivative.

When first deposited, the parylene or parylene derivative is thought to form a network resembling a fibrous mesh, with relatively large pores. As more is deposited, the porous layer **20** not only becomes thicker, but it is believed that parylene or parylene derivative is also deposited in the previously formed pores, making the existing pores smaller. Careful and precise control over the deposition of the parylene or parylene derivative therefore permits close control over the release rate of material from the at least one layer **18** of bioactive material. It is for this reason that the bioactive material lies under the at least one porous layer **20**, rather than being dispersed within or throughout it. The porous layer **20**, however, also protects the bioactive material layer **18** during deployment of the device **10**, for example, during insertion of the device **10** through a catheter and into the vascular system or elsewhere in the patient.

As shown in FIG. **1**, the device **10** of the present invention can further comprise at least one additional coating layer **16** posited between the structure **12** and the at least one layer **18** of bioactive material. While the additional coating layer **16** can simply be a medical grade primer, the additional coating layer **16** is preferably composed of the same polymer as the at least one porous layer **20**. However, the additional coating layer **16** is also preferably less porous than the at least one porous layer **20**, and is more preferably substantially nonporous. "Substantially nonporous" means that the additional coating layer **16** is sufficiently impervious to prevent any appreciable interaction between the base material **14** of the structure **12** and the blood to which the device **10** will be exposed during use. The use of an additional coating layer **16** which is substantially nonporous would permit the use of a toxic or poisonous base material **14**, as mentioned above. Even if the base material **14** of the structure **12** is biocompatible, however, it may be advantageous to isolate it from the blood by use of a substantially nonporous coating layer **16**.

Other polymer systems that may find application within the scope of the invention include polymers derived from photopolymerizable monomers such as liquid monomers preferably having at least two cross linkable C—C (Carbon to Carbon) double bonds and being a non-gaseous addition polymerizable ethylenically unsaturated compound, having a boiling point above 100° C., at atmospheric pressure, a molecular weight of about 100–1500 and being capable of forming high molecular weight addition polymers readily. More preferably, the monomer is preferably an addition photopolymerizable polyethylenically unsaturated acrylic or methacrylic acid ester containing two or more acrylate or methacrylate groups per molecule or mixtures thereof. A few illustrative examples of such multifunctional acrylates are ethylene glycol diacrylate, ethylene glycol dimethacrylate, trimethylopropane triacrylate, trimethylopropane trimethacrylate, pentaerythritol tetraacrylate or pentaerythritol tetramethacrylate, 1,6-hexanediol dimethacrylate, and diethyleneglycol dimethacrylate.

Also useful in some special instances are monoacrylates such as n-butyl-acrylate, n-butyl methacrylate, 2-ethylhexyl acrylate, lauryl-acrylate, and 2-hydroxy-propyl acrylate. Small quantities of amides of (meth)acrylic acid such as N-methylol methacrylamide butyl ether are also suitable, N-vinyl compounds such as N-vinyl pyrrolidone, vinyl esters of aliphatic monocarboxylic acids such as vinyl oleate, vinyl ethers of diols such as butanediol-1, 4-divinyl ether and allyl ether and allyl ester are also suitable. Also included would be other monomers such as the reaction products of di- or polyepoxides such as butanediol-1, 4-diglycidyl ether or bisphenol A diglycidyl ether with (meth)acrylic acid. The characteristics of the photopolymerizable liquid dispersing medium can be modified for the specific purpose by a suitable selection of monomers or mixtures thereof.

Other useful polymer systems include a polymer that is biocompatible and minimizes irritation to the vessel wall when the stent is implanted. The polymer may be either a biostable or a bioabsorbable polymer depending on the desired rate of release or the desired degree of polymer stability, but a bioabsorbable polymer is preferred for this embodiment since, unlike a biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Bioabsorbable polymers that could be used include poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters) (e.g., PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, biostable polymers with a relatively low chronic tissue response such as polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the stent such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins, polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

While plasma deposition and vapor phase deposition may be a preferred method for applying the various coatings on the stent surfaces, other techniques may be employed. For example, a polymer solution may be applied to the stent and the solvent allowed to evaporate, thereby leaving on the stent surface a coating of the polymer and the therapeutic substance. Typically, the solution can be applied to the stent by either spraying the solution onto the stent or immersing the stent in the solution. Whether one chooses application by immersion or application by spraying depends principally on the viscosity and surface tension of the solution, however, it has been found that spraying in a fine spray such as that available from an airbrush will provide a coating with the greatest uniformity and will provide the greatest control over the amount of coating material to be applied to the stent. In either a coating applied by spraying or by immersion, multiple application steps are generally desirable to provide improved coating uniformity and improved control over the amount of therapeutic substance to be applied to the stent.

When the layer **18** of bioactive material contains a relatively soluble material such as heparin, and when the at least one porous layer **20** is composed of parylene or a parylene derivative, the at least one porous layer **20** is preferably about 5,000 to 250,000 Å thick, more preferably about 5,000 to 100,000 Å thick, and optimally about 50,000 Å thick. When the at least one additional coating layer **16** is composed of parylene or a parylene derivative, the at least one additional coating is preferably about 50,000 to 500,000 Å thick, more preferably about 100,000 to 500,000 Å thick, and optimally about 200,000 Å thick.

When the at least one layer **18** of bioactive material contains a relatively soluble material such as heparin, the at least one layer **18** preferably contains a total of about 0.1 to 4 mg of bioactive material per cm^2 of the gross surface area of the structure **12**. This provides a release rate for the heparin (measured in vitro) which is desirably in the range of 0.1 to 0.5 mg/cm^2 per day, and preferably about 0.25 mg/cm^2 per day, under typical blood flows through vascular stents. It should be noted that the solubility of dexamethasone can be adjusted as desired, with or without the inclusion of heparin, by mixing it with one or more of its relatively more soluble derivatives, such as dexamethasone sodium phosphate.

FIG. **11** depicts another aspect of device **10** of the present invention in which coating layer **16** is applied directly to the outer surface of base material **14** of structure **12**. In this configuration, coating layer **16** is preferably a non-porous coating layer as previously described. When coating layer **16** comprises a parylene derivative, non-porous coating layer **16** ranges in thickness from 50,000 to 500,000 Å, more preferrably in the range of 100,000 to 500,000 Å, and optimally about 200,000 Å. In this aspect of the invention, non-porous coating layer **16** is also an adsorbent in which an adsorbent is defined as an agent that attracts other materials or particles to its surface as indicated in Dorland's Illustrated Medical Dictionary 26th Edition by W. B. Saunders Co., Philadelphia, Pa. Bioactive material **18** is then attached to the surface of coating layer **16**. An additional coating layer **20** can be applied over bioactive material layer **18**. Alternatively, alternating layers of coating material and the same or different bioactive materials can be applied to the surface of bioactive material layer **18**. However, in this particular aspect of the invention, the outer layer of structure **12** is a bioactive material layer **18**.

In still another aspect of the present invention as depicted in FIG. **11**, coating layer **16** can be considered an adsorbent layer and/or an absorbent layer in which a bioactive material is attached thereto. In one particular example, device **10** is a stainless steel GR II™ stent in which the stainless steel base material **14** of structure **12** is coated with a polymer and, in particular, parylene. This adsorbent polymer layer **16** of parylene is approximately 230,000 Å thick. Bioactive material layer **18** of the antiplatelet GP IIb/IIIa antibody (AZ1) was passively loaded on adsorbent polymer layer **16**. The polymer coated stainless steel stents were immersed for approximately 24 hours in a buffered aqueous solution of AZ1 antibody (1 mg/ml, pH=7.2) at 37° C. AZ1 is a monoclonal anti-rabbit platelet glycoprotein (GP) IIb/IIIa antibody. Using radio-labeled AZ1, it was demonstrated that approximately 0.02 μg antibody was loaded per mm^2 stent surface area (approximately 2 μg total for a 3×20 mm GR II™ stent). it was also demonstrated that in an in-vitro flow system (10 ml/min, 1% BSA in PBS) approximately half the loaded antibody remained on the stent after approximately 10 days perfusion.

The mechanism by which the stent is loaded with drug are thought to include adsorption onto the surface of the polymer layer and/or absorption into the polymer.

Previous studies with similar loading and release of AZ1 from cellulose coated stainless steel stents showed inhibition of platelet aggregation and reduced thrombosis rates in a rabbit model of deep arterial injury. (Aggarwal et al., *Antithrombotic Potential of Polymer-Coated Stents Eluting Platelet Glycoprotein IIb/IIIa Receptor Antibody,* American Heart Association Circulation Vol. 94 No. 12, Dec. 15, 1996, pp3311–3317).

In another example, c7E3 Fab as bioactive material layer **18** is attached to polymer coating layer **16**. Bioactive material c7E3 Fab is a chimeric monoclonal antibody that acts upon the Gp IIa/IIIb integrin on platelets to inhibit their aggregation. This antibody or receptor blocker can be used in humans intravenously to prevent thrombosis during coronary angioplasty. This receptor blocker is also known as ReoPro™ available from Eli Lilly, Indianapolis, Ind. Bioactive material layer **18** of the antiplatelet GP IIb/IIIa antibody (c7E3 Fab) was passively loaded on adsorbent polymer layer **16**. The polymer coated stainless steel stents were immersed for approximately 24 hours in a buffered aqueous solution of c7E3 Fab antibody (1 mg/ml, pH=7.2) at 37° C. c7E3 Fab is an inhibitor of platelet thrombus in humans. Using radio-labeled c7E3 Fab, it was demonstrated that approximately 0.10 μg antibody was loaded per mm^2 stent surface area (approximately 10 μg total for a 3×20 mm GR II™ stent). It was also demonstrated that in an in-vitro flow system (10 ml/min, 1% BSA in PBS) approximately half the loaded antibody remained on the stent after approximately 10 days perfusion. As is known, the extent of adsorption depends on the temperature as well as the surface area of the adsorbent. There are basically two kinds of adsorption: physical adsorption (also referred to as physisorption) and chemical adsorption (also referred to as chemisorption). The forces in physisorption are low between the adsorbent surface and the adsorbate molecules. The energies of adsorption are generally less than 3 kJ mol$^{31\ 1}$. Physisorption is usually reversible. The binding forces in chemisorption are much stronger than in physisorption, and the energies of adsorption range up to 400 kJ mol^{-1}. Chemisorption is much less reversible than physisorption. The adsorption of c7E3 Fab on adsorbent polymer layer **16** is believed to be chemisorption.

In another example, paclitaxel coated coronary stents have exhibited the potential to reduce proliferation. Mechanisms of restenosis include chronic remodeling and neointimal hyperplasia. Metallic stents can prevent chronic remodeling. However, because stents can actually promote neointimal hyperplasia, successful prevention of restenosis can require combined therapy of stents and antiproliferative agents. Among various means of antiproliferative therapy, drugs released from a stent coating seem attractive.

Among antiproliferative agents, paclitaxel, an antimicrotubule agent, has been found to reduce smooth muscle cell proliferation and migration and can be used as or in bioactive material layer **18**. Its mechanism of action involves promotion of abnormally stable and non-functional microtubule polymerization. Its efficacy in preventing neointimal hyperplasia has been demonstrated in smooth muscle cell culture studies and in several animal models of balloon injury when administered either locally or systemically.

More recently, paclitaxel coated stents have also been shown to reduce neointimal hyperplasia in a porcine coronary in-stent restenosis model. It has been shown that GR II™ stents coated with "slow-release" paclitaxel (175–200 μg total drug with in vitro release kinetics of 0.75 μg/day for the first 30 days) significantly reduced in-stent restenosis compared with controls (Table 1). Furthermore, the coating itself appears biocompatible. The adsorption of paclitaxel on base material **14** or on adsorbent polymer layer **16** is believed to be physisorption.

TABLE 1

Paclitaxel-Coated Stents versus Control

	Control (N = 10)	Paclitaxel-Coated Stent (N = 9)
Reference Vessel Diameter (mm)	2.9 ± 0.3	3.0 ± 0.2
Stent/Artery	1.1 ± 0.1	1.1 ± 0.1
Diameter Stenosis (%)	51 ± 27	27 ± 27*
Neointima Area (μm)	669 ± 357	403 ± 197*

*p < 0.05 versus control

Subsequent study data with two doses of "fast-release" paclitaxel showed that both "low-dose" and "high-dose" paclitaxel-coated stents significantly reduced in-stent restenosis compared to control stents (Table 2).

TABLE 2

Low-Dose and High-Dose Paclitaxel-Coated Stents versus Control

	Control (N = 12)	Low-Dose Paclitaxel (N – 10)	High-Dose Paclitaxel (N = 11)
Reference Vessel Diameter (mm)	2.8 ± 0.2	2.8 ± 0.7	3.0 ± 0.3
Stent/Artery	1.16 ± 0.09	1.15 ± 0.07	1.14 ± 0.05
Area Stenosis (%)	34.8 ± 15.6	19.3 ± 9.45*	15.1 ± 6.61*†
Neointima Area (μm)	1.52 ± 0.78	1.07 ± 0.53	0.93 ± 0.5*†

*p < 0.05 versus control

†p = Not significant versus low-dose paclitaxel

The results of these studies suggest that paclitaxel-coated stents can possibly and effectively prevent restenosis by eliminating geometric remodeling and reducing neointimal hyperplasia. These findings are especially important for high-risk lesion subsets, such as aorto-ostial lesions or small vessel, and can not only improve the long-terms results of stents but also extend the indications for stent implantation. These studies were conducted with coating layer **16** of, for example, parylene ranging in thickness from preferrably 10 to 1000 kÅ, more preferrably 20 to 250 kÅ, and even more preferrably 230 kÅ. It is also submitted that concentrations of paclitaxel can be posited on base material **14** or adsorbent polymer layer **16**. These concentrations can range from 0.6 mg/mm^2 to 60 mg/mm^2, preferably 1.5 mg/mm^2 to 5 mg/mm^2, and more preferably 1.8 mg/mm^2. Paclitaxel has low solubility in water, but may be taken up by tissue proteins and lipids when in contact therewith.

Included herein is a summary of animal studies involving paclitaxel coated coronary stents to reduce hyperplasia. In these studies, the implanted medical devices included a bioactive material having cytotoxic properties as evidence by the use of paclitaxel on the coronary stents.

One-month pig studies were performed to compare the results of stenting using standard 3.0x12 mm coronary stents (controls) to results obtained using 3.0x12 mm stents coated with various amounts of paclitaxel. These studies have revealed no safety problems related to the stents, and provide compelling evidence that paclitaxel, when coated on a stent in an adequate amount, helps maintain patency by inhibiting in-stent restenosis.

Juvenile domestic swine received one stent in the left anterior descending coronary artery (LAD) and/or one stent in the left circumflex (LCX) or right coronary arteries (RCA). To account for differences in vessel diameter prior to stenting, the deployment pressure for each stent was adjusted to achieve a balloon-to-artery ratio (BAR) of approximately 1.1–1.2. The pigs were followed for 1 month after stent implantation.

The pigs were fed a standard high fiber diet without lipid or cholesterol supplementation. For antiplatelet effect, each pig was administered approximately 325 mg aspirin and 250 mg ticlopidine daily, starting at least 2 days prior to surgery and continuing until the end of the study. Each pig was also administered approximately 10,000 units heparin during stent implantation and approximately 10,000 units heparin during follow-up angiography. No other antiplatelet agents or anticoagulants were given.

Angiograms were recorded immediately before stent implantation, immediately after stent implantation and at 1 month follow-up. Immediately after the follow-up angiography, the hearts were excised and the coronary vasculature was perfusion fixed at physiologic pressure. The vessels were then processed to obtain histologic cross sections for morphometric analysis from proximal, middle and distal locations within each stent.

Computer assisted quantitative coronary angiography (QCA) analysis and histomorphometric analysis were performed on each stented artery. Qualitative histopathologic analysis was also performed, with each artery evaluated for both injury and inflammation.

Table 3 presents an overview of the studies which included 4 groups categorized by the amount of paclitaxel on the stent and whether or not the paclitaxel was covered with a porous layer of parylene (0 μg paclitaxel–control, 35 μg paclitaxel, 85 μg paclitaxel and 400 μg paclitaxel+parylene N). Only 2 of the 19 pigs died prior to completing these studies. One pig in the 5 μg paclitaxel group died approximately 1 hour post-procedure, and one pig in the 15 μg paclitaxel group died approximately 17 days post-procedure.

TABLE 3

Overview (PN = Parylene N)

Paclitaxel (μg)	Stents Implanted	Premature Deaths	Stents Available for Analysis
0	6	None	6
5	8	One pig (stents in LAD & LCX) died at ≈ 1 hour	6
15	8*	One pig (stents in LAD & LCX) died at ≈ 17 days	4
35	5	None	5
85	5	None	5
400 + parylene N	6	None	6

*At 1 month follow-up, 2 stents were totally occluded by fibrovascular tissue, precluding angiographic or morphometric analyses.

Table 4 presents the procedural and follow-up QCA results for the studies. The 3 treatment groups with the highest amount of paclitaxel (i.e., 35 μg paclitaxel, 85 μg paclitaxel and 400 μg paclitaxel+parylene N) had Mean Diameter at Follow-up and MLD at Follow-up that were significantly greater than those of the respective control groups. As a result, Late Loss for the treatment groups with the highest amounts of paclitaxel was significantly less than that for the controls. The two treatment groups with the least amount of paclitaxel (i.e., 5 μg and 15 μg total paclitaxel coating) showed no significant difference in results compared to control. Thus, these studies suggest that there is a dose response effect, or at least a minimum amount required, for paclitaxel to inhibit in-stent restenosis.

Table 5 presents the quantitative histomorphometric results for the three one-month studies. These results are consistent with the quantitative angiographic results. The Lumen Diameter and the vessel Outer Diameter for the 3 highest paclitaxel groups were greater than for their respective controls; however, only the results for the 85 μg paclitaxel and 400 μg paclitaxel+parylene N groups were consistently significantly greater. The 85 μg paclitaxel and 400 μg paclitaxel+parylene N groups showed significantly less vessel Wall Thickness and Neointimal Thickness than control. The Wall Thickness and Neointimal Thickness results for the stents with the next highest amount of paclitaxel (35 μg) tended to be less than the controls, but did not reach statistical significance for either measure.

Histopathology has revealed no substantial differences in inflammatory response to the paclitaxel-coated or control stents. Occasional small patches of luminal fibrin were observed in approximately 50% of the histologic sections from the 400 μg paclitaxel+parylene N, 85 μg paclitaxel and 35 μg paclitaxel stents and in none of the sections from either the 15 μg paclitaxel stents, the 5 μg paclitaxel stents, or the control coronary stents. Vessel wall hypocellularity and hyalinization have also been observed in over 80% of the histologic sections from the 400 μg paclitaxel+parylene N, 85 μg paclitaxel and 35 μg paclitaxel stents, approximately 67% of the sections from the 15 μg paclitaxel stents, approximately 28% of the sections from the 5 μg paclitaxel stents, and less than 10% of the sections from the control coronary stents. These findings were not associated with any clinical sequelae in these 1-month studies.

TABLE 4

One-Month QCA Data (Mean ± Standard Deviation)

Paclitaxel (μg)	Mean Diameter Pre-procedure (mm)	BAR	Mean Diameter at Follow-up (mm)	MLD at F/U (mm)	Late Loss (%)
0	2.80 ± 0.14	1.19 ± 0.04	2.18 ± 0.30	1.91 ± 0.24	19.5 ± 11.7
5	2.86 ± 0.18	1.19 ± 0.05	2.23 ± 0.51	1.74 ± 0.45	17.9 ± 20.3
15	2.81 ± 0.14	1.22 ± 0.04	2.15 ± 0.43	1.90 ± 0.38	20.1 ± 19.9
35	2.74 ± 0.11	1.20 ± 0.04	2.62 ± 0.21	2.42 ± 0.25	2.6 ± 7.5
85	2.85 ± 0.15	1.20 ± 0.06	2.77 ± 0.22	2.61 ± 0.15	1.6 ± 8.1
400 + parylененN	2.99 ± 0.22	1.12 ± 0.06	2.92 ± 0.22	2.75 ± 0.17	0.32 ± 7.1

TABLE 5

Histomorphometric Data at 1-month F/U (Means ± Standard Deviation)

Paclitaxel (μg)	Lumen Diameter (mm)	Outer Diameter (mm)	Wall Thickness (mm)	Neointimal Thickness (mm)
0	1.87 ± 0.31	2.70 ± 0.24	0.41 ± 0.18	0.24 ± 0.12
5	1.77 ± 0.34	2.73 ± 0.28	0.48 ± 0.23	0.31 ± 0.20
15	1.87 ± 0.37	2.41 ± 0.90	0.46 ± 0.22	0.29 ± 0.19
35	2.12 ± 0.52	2.78 ± 0.32	0.33 ± 0.17	0.19 ± 0.16
85	2.40 ± 0.31	2.96 ± 0.31	0.28 ± 0.10	0.15 ± 0.08
400 + paryleneN	2.58 ± 0.19	3.06 ± 0.17	0.24 ± 0.07	0.12 ± 0.06

The implantable medical device of the invention has been described using a structure such as a stent adapted for introduction into a patient. The structure **12** is composed of a base material **14** and has at least one surface. The surface of the base material has an inherent surface energy density outside the range of 20 to 30 dynes per cm^2 so as to promote the adherence of a bioactive material thereon. Studies by Baird have indicated that the range of 20 to 30 dynes per cm^2 minimizes the adherence of material such as organisms thereon or thereto. Depending on the base material selected, the surface energy density is selected to maximize the adherence of the bioactive material posited thereon. Depending on the base material selected such as stainless steel, the inherent surface energy density may be increased by commercial ion beam bombardment and/or deposition. The surface treatment is performed to again maximize the adherence of the bioactive material posited on the base material.

With respect to the bioactive material posited on the surface of the structure, a bioactive material having cytotoxic properties is selected to minimize hyperplasia. The aformentioned studies were performed using paclitaxel as a bioactive material having cytotoxic properties. The paclitaxel can be utilized by itself or in combination with other anti-cancer, anti-neoplastic, or other chemotherapeutic agents. The use of a bioactive material having cytotoxic properties is clearly in opposition to present day thinking where the use of cytotoxic materials is not at all encouraged or even prohibited.

FIG. **12** depicts still another aspect of device **10** of FIG. **11**. In this embodiment, a parylene adhesion promotion layer **30** is first applied to stainless steel base material **14** of structure **12**. By way of example, adhesion promotion layer **30** is a thin layer of silane having a thickness in the range of, for example, 0.5 to 5,000 Å and preferrably, 2 to 50 Å. This silane promotion layer is preferrably A-174 silane including a gamma-methacryloxypropytrimethoxysilane, which is available from Specialty Coating Systems Inc., Indianapolis, Ind. In preparing the outer surface of base material **14**, it is first cleaned with isopropyl alcohol. The stent is then dipped in the silane to apply a very thin layer thereof to the outer surface of the base material. Polymer coating layer **16** of parylene is then applied to the silane layer. Other methods of preparing the outer surface of base material **14** include plasma etching and grit blasting. Preparation includes cleaning the outer surface of the base material with isopropyl alcohol, plasma etching the outer surface of the base material and applying the silane to the plasma etched surface. With grit blasting, the outer surface of the base material is grit blasted and then cleaned with isopropyl alcohol to which silane is applied to the cleansed grit blasted surface.

As shown in FIG. **2**, the device **10** of the present invention is not limited to the inclusion of a single layer **18** of bioactive material. The device **10** can, for example, comprise a second layer **22** of a bioactive material posited over the structure **12**. The bioactive material of the second layer **22** can be, but need not necessarily be, different from the bioactive material of the first bioactive material layer **18**, only that they not be posited on the same surface of the device **10** without the intermediate porous layer **24**. The use of different materials in the layers **18** and **22** allows the device **10** to perform more than a single therapeutic function.

The device **10** of the present invention can further comprise an additional porous layer **24** of the polymer posited between each of the layers **18** and **22** of bioactive material. It is reiterated that bioactive material **18** is on one surface of structure **12**. The other surface may be free of bioactive material or may comprise one or more different bioactive materials. The additional porous layer **24** can give the bioactive materials in the layers **18** and **22** different release rates. Simultaneously, or alternatively, the device **10** may employ bioactive materials in the two layers **18** and **22** which are different from one another and have different solubilities. In such a case, it is advantageous and preferred to position the layer **22** containing the less soluble bioactive material above the layer **18** containing the more soluble bioactive material. Alternatively, the bioactive material **18** may be contained in holes, wells, slots and the like occurring within the stent surface as illustrated in FIGS. **8–10** and will further be discussed in greater detail.

For example, when the structure **12** of the device **10** is configured as a vascular stent, it is advantageous for the at least one layer **18** to contain relatively soluble heparin, and the second layer **22** to contain relatively less soluble dexamethasone. Unexpectedly, the heparin promotes the release of the dexamethasone, increasing its release rate many times over the release rate of dexamethasone in the absence of heparin. The release rate of the heparin is also lowered, somewhat less dramatically than the increase of the dexamethasone release rate. More particularly, when dexamethasone is disposed by itself beneath a porous parylene layer **20** dimensioned as disclosed above, its release rate is negligible; an adequate release rate is obtained only when the thickness of the porous layer **20** is reduced by a factor of ten or more. In contrast, when a layer **22** of dexamethasone is disposed over a layer **18** of heparin, and beneath a porous parylene layer **20** dimensioned as above, the dexamethasone may be released at a desirable rate of about 1 to 10 μg/cm^2 per day. Moreover, and even more unexpectedly, this increased release rate for the dexamethasone is thought to be maintained even after all of the heparin has been released from the layer **18**.

The bioactive material layers **18** and/or **22** are applied to the device **10** independent of the application of the porous polymer layers **20** and/or **24**. Any mixing of a bioactive material from the layers **18** and/or **22** into the porous layers **20** and/or **24**, prior to introducing the device **10** into the vascular system of the patient, is unintentional and merely incidental. This gives significantly more control over the release rate of the bioactive material than the simple dispersal of a bioactive material in a polymeric layer.

The device **10** need not include the additional porous layer **24** when two or more layers **18** and **22** of bioactive material are present. As shown in FIG. **3**, the layers **18** and **22** do not have to be separated by a porous layer, but can instead lie directly against one another. It is still advantageous in this embodiment to position the layer **22** containing the relatively less soluble bioactive material above the layer **18** containing the relatively more soluble bioactive material.

Whether or not the additional porous layer **24** is present, it is preferred that the layers **18** and **22** contain about 0.05 to 2.0 mg of each of heparin and dexamethasone, respectively, per 1 cm^2 of the gross surface area of the structure **12**. The total amount of bioactive material posited in the layers **18** and **22** over the structure **12** is thus preferably in the range of about 0.1 to 10 mg/cm^2.

Some dexamethasone derivatives, such as dexamethasone sodium phosphate, are substantially more soluble than dexamethasone itself. If a more soluble dexamethasone derivative is used as the bioactive material in the device **10** of the present invention, the thickness of the at least one porous layer **20** (and of the additional porous layer **24**) should be adjusted accordingly.

The particular structure of the device **10** as disclosed may be adapted to specific uses in a variety of ways. For example, the device **10** may include further layers of the same or different bioactive materials. These additional layers of bioactive material may or may not be separated by additional porous layers, as convenient or desired. Alternatively, additional porous layers may separate only some of the additional layers of bioactive material. Moreover, one bioactive material may be placed on one portion of the structure **12** of the device **10**, and another bioactive material placed on a different portion of the structure **12** of the device **10**.

Alternatively, the device **10** need not include the additional coating layer **16** at all. Such a configuration is shown in FIG. **4**, in which the bioactive material layer **18** is posited directly atop the base material **14** of the structure **12**. In such a case, it may be highly advantageous to surface process or surface activate the base material **14**, to promote the deposition or adhesion of the bioactive material on the base material **14**, especially before the depositing of the at least one porous layer **20**. Surface processing and surface activation can also selectively alter the release rate of the bioactive material. Such processing can also be used to promote the deposition or adhesion of the additional coating layer **16**, if present, on the base material **14**. The additional coating layer **16** itself, or any second or additional porous layer **24** itself, can similarly be processed to promote the deposition or adhesion of the bioactive material layer **18**, or to further control the release rate of the bioactive material.

Useful methods of surface processing can include any of a variety of such procedures, including: cleaning; physical modifications such as etching, drilling, cutting, or abrasion; and chemical modifications such as solvent treatment, the application of primer coatings, the application of surfactants, plasma treatment, ion bombardment and covalent bonding.

It has been found particularly advantageous to plasma treat the additional coating layer **16** (for example, of parylene) before depositing the bioactive material layer **18** atop it. The plasma treatment improves the adhesion of the bioactive material, increases the amount of bioactive material that can be deposited, and allows the bioactive material to be deposited in a more uniform layer. Indeed, it is very difficult to deposit a hygroscopic agent such as heparin on an unmodified parylene surface, which is hydrophobic and poorly wettable. However, plasma treatment renders the parylene surface wettable, allowing heparin to be easily deposited on it.

Any of the porous polymer layers **20** and **24** may also be surface processed by any of the methods mentioned above to alter the release rate of the bioactive material or materials, and/or otherwise improve the biocompatibility of the surface of the layers. For example, the application of an overcoat of polyethylene oxide, phosphatidylcholine or a covalently bound bioactive material, e.g., covalently attached heparin to the layers **20** and/or **24** could render the surface of the layers more blood compatible. Similarly, the plasma treatment or application of a hydrogel coating to the layers **20** and/or **24** could alter their surface energies, preferably providing surface energies in the range of 20 to 30 dynes/cm^2, thereby rendering their surfaces more biocompatible.

Referring now to FIG. **5**, an embodiment of the device **10** is there shown in which a mechanical bond or connector **26** is provided between (a) any one of the porous layers **20** and **24**, and (b) any or all of the other of the porous layers **20** and **24**, the additional coating layer **16** and the base material **14**. The connector **26** reliably secures the layers **16**, **20** and/or **24** to each other, and or to the base material **14**. The connector **26** lends structural integrity to the device **10**, particularly after the bioactive material layer or layers **18** and/or **20** have been fully released into the patient.

For simplicity, the connector **26** is shown in FIG. **5** as a plurality of projections of the base material **14** securing a single porous layer **20** to the base material **14**. The connector **26** may alternatively extend from the porous layer **20**, through the bioactive material layer **18**, and to the base material **14**. In either case, a single layer **18** of bioactive material, divided into several segments by the connector **26**, is posited between the porous layer **20** and the base material **14**. The connectors can also function to partition the different bioactive agents into different regions of the device's surface.

The connector **26** may be provided in a variety of ways. For example, the connector **26** can be formed as a single piece with the base material **14** during its initial fabrication or molding into the structure **12**. The connector **26** can instead be formed as a distinct element, such as a bridge, strut, pin or stud added to an existing structure **12**. The connector **26** can also be formed as a built-up land, shoulder, plateau, pod or pan on the base material **14**. Alternatively, a portion of the base material **14** between the desired locations of plural connectors **26** may be removed by etching, mechanical abrasion, or the like, and the bioactive material layer **18** deposited between them. The connector **26** can also be formed so as to extend downwards towards the base material **14**, by wiping or etching away a portion of a previously applied bioactive material layer **18**, and allowing the porous layer **20** to deposit by vapor deposition or plasma deposition directly on the bare portions of the base material **14**. Other ways to expose a portion of the base material **14** to direct connection to the porous layer **20** will be evident to those skilled in this area.

In another preferred embodiment, as illustrated in FIGS. **6**A, **6**B and **7**, a bioactive material **18** is posited on the one surface of base material **14** making up structure **12** in FIG. **6**A. FIG. **7** shows a stent **10** in its flat or planar state prior to being coiled and showing porous layer **20** applied to its outermost surface. FIGS. **6**A and **6**B are section views along line **6**—**6** of FIG. **7**. The bioactive material **18** posited on the one surface of base material **14** in FIG. **6**A may be a number of different therapeutic and/or diagnostic agents. For example, the device **10** may be a stent which is placed in the body of a patient near a tumor to deliver a chemotherapeutic agent, such as tamoxifen citrate or Taxol®, directly to the tumor. A porous layer **20** is posited over the bioactive material **18** to provide a smoother surface as well as a more controlled release of the bioactive material **18**. As further illustrated in FIG. **6**A, the opposite surface of the device may have, for example, heparin **18'** covalently bonded to porous layer **20**, particularly where this surface faces, for example, the lumen of a blood vessel, to provide antithrombotic effect and blood compatibility. It is pointed out, as has been discussed herein, a third but different bioactive material may be posited (not shown) on the opposite surface of base material **14** from the first bioactive material **18** and on the same side of base material **14** as the covalently bound heparin or any other bioactive material including other covalently bound bioactive materials and separated by porous layer **20**.

A variation of the embodiment shown in FIG. **6**A is illustrated in FIG. **6**B, where two bioactive materials **18** and **18'** are posited on the same surface of based material **14** of structure **12**. A porous layer **20** may be deposited over the bioactive materials **18** and **18'** as well as the bioactive-material-free surface of base material **14**. This embodiment illustrates a situation where it may be desirable to deliver two agents to the tissue to which the particular surface of device **10** is exposed, e.g., an antiinflammatory agent and an antiviral agent. Moreover, the opposite surface of the device free of bioactive material is available for positing one or more bioactive materials or therapeutic agents, e.g., an antithrombotic agent.

As has been previously discussed, multiple layers of bioactive materials and porous layers may be applied to the device **10** where the limiting factors become the total thickness of the device, the adhesion of multiple layers and the like.

In still another embodiment of the present invention, the device of the present invention includes apertures within the device for containing the bioactive material. This embodiment is illustrated in FIGS. **8**, **9**, **10**A, **10**B, **10**C and **10**D. FIG. **8** shows an arm of the stent of FIG. **7** wherein the arm includes holes **28** into which a bioactive material is contained. FIG. **9** shows a section of the arm of the stent along lines **9**—**9** of FIG. **8**. Bioactive material **18** is contained within the hole **28** where the base material **14** contains coating **16** and further where porous layer **20** forms the outer most layer for the bioactive material **18** to diffuse through. In an alternative embodiment, wells **28'** may be cut, etched or stamped into the base material **14** of the device in which a bioactive material **18** may be contained. This embodiment is illustrated in FIGS. **10**A, **10**B, **10**C and **10**D which are sectional FIGs. taken along line **10**—**10** of FIG. **8**. The wells **28'** may also be in the form of slots or grooves in the surface of the base material **14** of the medical device. This aspect of the invention provides the advantage of better controlling the total amount of the bioactive material **18** to be released as well as the rate at which it is released. For example, a V-shape well **28'**, as illustrated in FIG. **10**D, will contain less quantity of bioactive material **18** and release the material at geometric rate as compared to a square shaped well **28'**, as illustrated in FIG. **10**B, which will have a more uniform, linear release rate.

The holes, wells, slots, grooves and the like, described above, may be formed in the surface of the device **10** by a variety of techniques. For example, such techniques include drilling or cutting by utilizing lasers, electron-beam machining and the like or employing photoresist procedures and etching the desired apertures.

All the bioactive materials discussed above that may be coated on the surface of the device **10** may be used to be contained within the apertures of this aspect of the invention. Likewise, layers of bioactive materials and porous layers may be applied and built up on the exterior surfaces of the device as described previously with regard to other aspects of the invention, e.g., heparin, may be covalently bound to one surface of the device illustrated in FIG. **9**.

The method of making the device **10** according to the present invention may now be understood. In its simplest form, the method comprises the steps of depositing the at least one layer **18** of bioactive material over the structure **12**, followed by depositing the at least one porous layer **20**, preferably by vapor deposition or plasma deposition, over the at least one bioactive material layer **18** on the one surface of structure **12**, the at least one porous layer **20** being composed of a biocompatible polymer and being of a thickness adequate to provide a controlled release of the bioactive material. Preferably, the at least one additional coating layer **16** is first posited by vapor deposition directly on the base material **14** of the structure **12**. Such deposition is carried out by preparing or obtaining di-p-xylylene or a derivative thereof, sublimating and cracking the di-p-xylylene or derivative to yield monomeric p-xylylene or a monomeric derivative, and allowing the monomer to simultaneously condense on and polymerize over the base material **14**. The deposition step is carried out under vacuum, and the base material **14** maintained at or near room temperature during the deposition step. The deposition is carried out in the absence of any solvent or catalyst for the polymer, and in the absence of any other action to aid polymerization. One preferred derivative for carrying out the deposition step is dichloro-di-p-xylylene. The parylene or parylene derivative is preferably applied at the thickness disclosed above, to yield a coating layer **16** which is substantially nonporous, but in any event less porous than the at least one porous layer **20** to be applied. If required by the composition of the coating layer **16**, the layer **16** is then surface processed in an appropriate manner, for example, by plasma treatment as disclosed above.

The at least one layer **18** of the desired bioactive material or materials is then applied to the one surface of the structure **12**, and in particular, onto the additional coating layer **16**. This application step can be carried out in any of a variety of convenient ways, such as by dipping, rolling, brushing or spraying a fluid mixture of the bioactive material onto the additional coating layer **16**, or by electrostatic deposition of either a fluid mixture or dry powder of the bioactive material, or by any other appropriate method. Different bioactive agents may be applied to different sections or surfaces of the device.

It can be particularly convenient to apply a mixture of the bioactive material or materials and a volatile fluid over the structure, and then remove the fluid in any suitable way, for example, by allowing it to evaporate. When heparin and/or dexamethasone or its derivatives serve as the bioactive material(s), the fluid is preferably ethyl alcohol. The bioactive material is preferably applied in an amount as disclosed above.

Other methods of depositing the bioactive material layer **18** over the structure **12** would be equally useful. Without regard to the method of application, however, what is important is that the bioactive material need only be physically held in place until the porous layer **20** is deposited over it. This can avoid the use of carriers, surfactants, chemical binding and other such methods often employed to hold a bioactive agent on other devices. The additives used in such methods may be toxic, or the additives or methods may alter or degrade the bioactive agent, rendering it less effective, or even toxic itself. Nonetheless, if desired these other methods may also be employed to deposit the bioactive material layer **18** of the present invention.

The bioactive material may, of course, be deposited on the one surface of the structure **12** as a smooth film or as a layer of particles. Moreover, multiple but different bioactive materials may be deposited in a manner that different surfaces of the device contain the different bioactive agents. In the latter case, the particle size may affect the properties or characteristics of the device **10**, such as the smoothness of the uppermost porous coating **20**, the profile of the device **10**, the surface area over which the bioactive material layer **18** is disposed, the release rate of the bioactive material, the formation of bumps or irregularities in the bioactive material layer **18**, the uniformity and strength of adhesion of the bioactive material layer **18**, and other properties or characteristics. For example, it has been useful to employ micronized bioactive materials, that is, materials which have been processed to a small particle size, typically less than 10 μm in diameter. However, the bioactive material may also be deposited as microencapsulated particles, dispersed in liposomes, adsorbed onto or absorbed into small carrier particles, or the like.

In still another embodiment according to the present invention, the bioactive material may be posited on the one surface of structure **12** in a specific geometric pattern. For example, the tips or arms of a stent may be free of bioactive material, or the bioactive material may be applied in parallel lines, particularly where two or more bioactive materials are applied to the same surface.

In any event, once the bioactive material layer **18** is in place, the at least one porous layer **20** is then applied over the at least one bioactive material layer **18** in the same manner as for the application of the at least one additional coating **16**. A polymer such as parylene or a parylene derivative is applied at the lesser thickness disclosed above, however, so as to yield the at least one porous layer **20**.

Any other layers, such as the second bioactive material layer **22** or the additional porous layer **24**, are applied in the appropriate order and in the same manner as disclosed above. The steps of the method are preferably carried out with any of the bioactive materials, structures, and base materials disclosed above.

Of course, polyimide may be deposited as any or all of the porous and additional coating layers **20**, **24** and/or **16** by vapor deposition in a manner similar to that disclosed above for parylene and its derivatives. Techniques for the plasma deposition of polymers such as poly(ethylene oxide), poly (ethylene glycol), poly(propylene oxide), silicone, or a polymer of methane, tetrafluoroethylene or tetramethyldisiloxane on other objects are well-known, and these techniques may be useful in the practice of the present invention.

Another technique for controlling the release of the bioactive material may include depositing monodispersed polymeric particles, i.e., referred to as porogens, on the surface of the device **10** comprising one or more bioactive materials prior to deposition of porous layer **20**. After the porous layer **20** is deposited and cured, the porogens may be dissolved away with the appropriate solvent, leaving a cavity or pore in the outer coating to facilitate the passage of the underlying bioactive materials.

The method of using the device **10** of the present invention in medically treating a human or veterinary patient can now be easily understood as well. The method of the present invention is an improvement over previous methods which include the step of inserting into a patient an implantable vascular device **10**, the device **10** comprising a structure **12** adapted for introduction into the vascular system of a patient, and the structure **12** being composed of a base material **14**. The method according to the present invention comprises the preliminary steps of depositing at least one layer **18** of a bioactive material on one surface of the structure **12**, followed by depositing at least one porous layer **20** over the at least one bioactive material layer **18**, the porous layer **20** being composed of a polymer and having a thickness adequate to provide a controlled release of the bioactive material when the device **10** is positioned in the patient's vascular system.

The method can further entail carrying out the two depositing steps with the various embodiments of the device

10 disclosed above, in accordance with the method of making the device **10** disclosed above. More particularly, the step of depositing the at least one porous layer **20** can comprise polymerizing the at least one layer **20** from a monomer vapor, preferably a vapor of parylene or a parylene derivative, free of any solvent or catalyst. The method can also comprise the step of depositing the at least one additional coating layer **16** between the structure **12** and the at least one bioactive material layer **18**.

The method of treatment according to the present invention is completed by inserting the device **10** into the vascular system of the patient. The at least one porous layer **20** and any additional porous layers **24** automatically release the bioactive material or materials in a controlled fashion into the patient.

The remaining details of the method of medical treatment are the same as those disclosed with respect to the method of making the device **10** of the present invention; for the sake of brevity, they need not be repeated here.

In view of the disclosure above, it is clear that the present invention provides an implantable medical device which achieves precise control over the release of one or more bioactive materials contained in the device. Moreover, the polyimide, parylene, parylene derivative or other polymeric layers **16**, **20** and/or **24** can be remarkably thin, in comparison to the thicknesses required for other polymer layers. The bulk or substantial majority of the overall coating on the structure **12** can therefore consist of bioactive material. This allows the supply of relatively large quantities of bioactive material to the patient, much greater than the amounts supplied by prior devices. These quantities of bioactive material can be supplied to any of a wide variety of locations within a patient during or after the performance of a medical procedure, but are especially useful for preventing abrupt closure and/or restenosis of a blood vessel by the delivery of an antithrombic or other medication to the region of it which has been opened by PTA. The invention permits the release rate of a bioactive material to be carefully controlled over both the short and long terms. Most importantly, any degradation of the bioactive material which might otherwise occur by other polymer coating techniques is avoided.

The other details of the construction or composition of the various elements of the disclosed embodiment of the present invention are not believed to be critical to the achievement of the advantages of the present invention, so long as the elements possess the strength or flexibility needed for them to perform as disclosed. The selection of these and other details of construction are believed to be well within the ability of one of ordinary skills in this area, in view of the present disclosure.

INDUSTRIAL APPLICABILITY

The present invention is useful in the performance of vascular surgical procedures, and therefore finds applicability in human and veterinary medicine.

It is to be understood, however, that the above-described device is merely an illustrative embodiment of the principles of this invention, and that other devices and methods for using them may be devised by those skilled in the art, without departing from the spirit and scope of the invention. It is also to be understood that the invention is directed to embodiments both comprising and consisting of the disclosed parts. It is contemplated that only part of a device need be coated. Furthermore, different parts of the device can be coated with different bioactive materials or coating layers. It is also contemplated that different sides or regions of the same part of a device can be coated with different bioactive materials or coating layers.

What is claimed is:

1. An implantable medical device (**10**), comprising:

a structure (**12**) adapted for introduction into a patient, the structure (**12**) having at least one surface and being composed of a base material (**14**);

at least one coating layer (**16**) posited on one surface of the structure (**12**); and

at least one layer (**18**) of a first bioactive material posited over at least a portion of the at least one coating layer (**16**), wherein said at least one coating layer (**16**) provides for a controlled release of the bioactive material from the at least one coating layer (**16**), and wherein said first bioactive material (**18**) comprises paclitaxel and has cytotoxic properties.

2. The device (**10**) of claim **1** wherein said coating layer has a surface energy density to increase adhesion of said first bioactive material to said coating layer.

3. The device (**10**) of claim **1** further comprising at least one porous layer (**20**) posited over the bioactive material layer (**18**), wherein said at least one porous layer (**20**) is composed of a polymer and said polymer provides for a controlled release of the bioactive material through said at least one porous layer.

4. The device (**10**) of claim **3**, wherein the non-porous material is at least one of an adsorbent material and an absorbent material.

5. The device (**10**) of claim **4**, wherein the at least one coating layer (**16**) of the adsorbent material has a thickness of approximately 230,000 Angtroms.

6. The device (**10**) of claim **1**, wherein the coating layer (**16**) comprises a non-porous material.

7. The device (**10**) of claim **1**, wherein the at least one coating layer (**16**) comprises a parylene derivative.

8. The device (**10**) of claim **7**, wherein the at least one coating layer (**16**) has a thickness in a range from 50,000 to 500,000 Angstroms.

9. The device (**10**) of claim **7**, wherein the at least one coating layer (**16**) has a thickness in a range from 100,00 to 500,000 Angstroms.

10. The device (**10**) of claim **7**, wherein the at least one coating layer (**16**) has a thickness of approximately 200,000 Angstroms.

11. The device (**10**) of claim **1**, wherein the bioactive material layer includes a chimeric monoclonal antibody.

12. The device (**10**) of claim **1**, wherein the polymer is selected from the group consisting of a polyamide, polymers of parylene or derivatives thereof, poly(ethylene oxide), poly(ethylene glycol), poly(propylene oxide), silicone based polymers, polymers of methane, tetrafluoroethylene or tetramethyidisiloxane or a polymer derived from photopolymerizeable monomers.

13. The device of claim **1**, wherein said paclitaxel is in a concentration of between 0.06 mg/mm^2 and 60 mg/mm^2.

14. The device of claim **1**, wherein said paclitaxel is in a concentration of between 1.5 mg/mm^2 and 5 mg/mm^2.

15. The device of claim **1**, wherein said paclitaxel is in a concentration of about 1.8 mg/mm^2.

16. The device of claim **1**, wherein said paclitaxel is in an amount of at least 35 μg.

17. The device of claim **1**, wherein said bioactive material includes at least 35 μg and includes at least up to a total of 400 μg of a mixture of paclitaxel and parylene N.

18. An implantable medical device (**10**), comprising:

a structure (**12**) adapted for introduction into a patient, the structure (**12**) having at least one surface and being comprised of a base material (**14**); and at least one layer (**18**) of a bioactive material having cytotoxic properties posited on the at least one surface of the structure (**12**), wherein said bioactive material (**18**) comprises paclitaxel.

19. The device (**10**) of claim **18**, wherein said at least one surface has been treated and has a surface energy density to increase adhesion of said bioactive material to said base material.

20. The device of claim **18**, wherein said paclitaxel is in a concentration of between 0.06 mg/mm^2 and 60 mg/mm^2.

21. The device of claim **18**, wherein said paclitaxel is in a concentration of between 1.5 mg/mm^2 and 5 mg/mm^2.

22. The device of claim **18**, wherein said paclitaxel is in a concentration of about 1.8 mg/mm^2.

23. The device of claim **18**, wherein said paclitaxel is in an amount of at least 35 μg.

24. The device of claim **18**, wherein said bioactive material includes at least 35 μg and includes at least up to a total of 400 μg of a mixture of paclitaxel and parylene N.

25. An implantable medical deice (**10**), comprising:

a structure (**12**) adapted for introduction into a patient, the structure (**12**) having at least one surface and being composed of a base material (**14**);

at least one adhesion promotion layer (**30**) posited on one surface of the structure (**12**); and

at least one layer (**18**) of a first bioactive material having cytotoxic properties posited over at least a portion of the at least one adhesion promotion layer (**30**), wherein said first bioactive material (**18**) comprises paclitaxel.

26. The device (**10**) of claim **25** further comprising at least one porous layer (**20**) posited over the bioactive material layer (**18**), wherein said at least one porous layer **20** includes a polymer and said polymer provides for a controlled release if the bioactive material thought said at least one porous layer.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,299,604 B1
DATED : October 9, 2001
INVENTOR(S) : Anthony O. Ragheb et al.

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [56], U.S. PATENT DOCUMENTS, delete "5,380,299", "Fearmot" and substitute -- Fearnot -- in its place.
OTHER PUBLICATIONS, "Ragheb et al.", -- " -- (opening quotes) before "Coated", and insert -- " -- (closing quotes) after "Device"; and insert -- patent -- before "application".
"LEXPAT KWIC site printout for U.S. Patent No. 5,194,303", delete "college" and substitute -- College -- in its place.

Column 3,
Line 28, immediately after "Å" delete "," (comma) and substitute -- . -- (period) in its place.

Column 13,
Line 48, after "stent)." delete "it" and substitute -- It -- in its place.

Column 14,
Line 26, delete "mol $^{31\ 1}$" and substitute -- mol^{-1} -- in its place.

Column 15,
Line 37, delete "long-terms" and substitute -- long-term in its place.
Lines 44-45, delete "mg/mm^2" (all occurrences) and substitute -- μg/mm^2 -- in its place (all occurrences).

Column 18,
Line 45, delete "methacryloxypropytrimethoxysilane," and substitute -- methacryloxypropyltrimethoxysilane, -- in its place.

Column 26,
Lines 54, 56 and 58, delete "mg/mm^2" (both occurrences) and substitute -- μg/mm^2 -- in its place (both occurrences).

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,299,604 B1
DATED : October 9, 2001
INVENTOR(S) : Anthony O. Ragheb et al.

Page 2 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27,
Line 9, 12 and 14, delete "mg/mm^2" (both occurrences) and substitute -- μg/mm^2 -- in its place (both occurrences).

Column 28,
Line 16, delete "if" and substitute -- of -- in its place, and after "material" delete "thought" and substitute -- through -- in its place.

Signed and Sealed this

Twelfth Day of August, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006517888B1

(12) **United States Patent**
Weber

(10) **Patent No.: US 6,517,888 B1**
(45) **Date of Patent: Feb. 11, 2003**

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(54) **METHOD FOR MANUFACTURING A MEDICAL DEVICE HAVING A COATED PORTION BY LASER ABLATION**

(75) Inventor: **Jan Weber**, Tuam (IR)

(73) Assignee: **Scimed Life Systems, Inc.**, Maple Grove, MN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/724,503**

(22) Filed: **Nov. 28, 2000**

(51) **Int. Cl.^{7}** **A61L 27/04**; A61L 27/00; A61L 27/06; A61L 27/28; B05D 3/06

(52) **U.S. Cl.** **427/2.24**; 427/2.28; 427/2.1; 427/553; 427/554; 427/555; 427/556; 427/307; 427/256; 427/287

(58) **Field of Search** 427/2.24, 2.28, 427/2.1, 553, 554, 555, 556, 307, 230, 239, 256, 287

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S. Nolte et al., *Polarization effects in ultrashort–pulse laser drilling*, Appl.Phys. A 68, 563–567 (1999).

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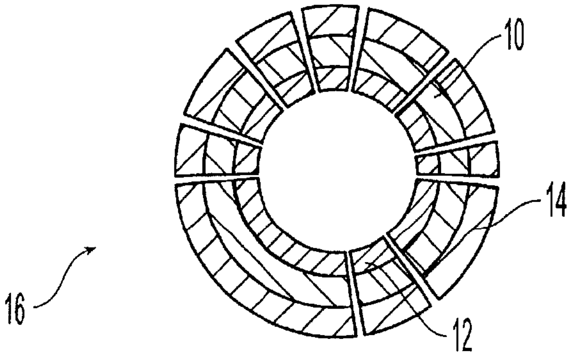
Primary Examiner—Shrive P. Beck
Assistant Examiner—Jennifer Kolb Michener
(74) *Attorney, Agent, or Firm*—Pennie & Edmonds LLP

(57) **ABSTRACT**

The present invention is directed to a method for manufacturing a medical device having a coated portion which comprises obtaining a structure having an inner surface and an outer surface; coating at least a portion of the inner or outer surface with a first coating material; and ablating the coated tubular structure with a laser to form at least one opening therein to form the coated portion. A plate can be used instead of the structure, and the plate is folded to form the structure after the ablation. A plurality of medical devices, made of any materials and having uniform coating (s), can be easily manufactured by the method of the present invention.

31 Claims, 2 Drawing Sheets



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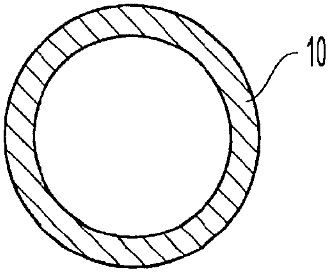

Fig. 1A

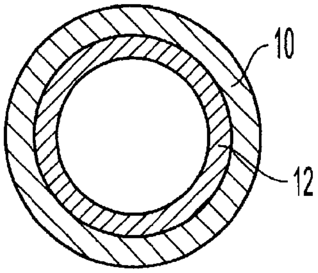

Fig. 1B

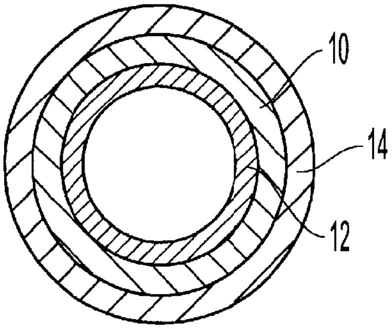

Fig. 1C

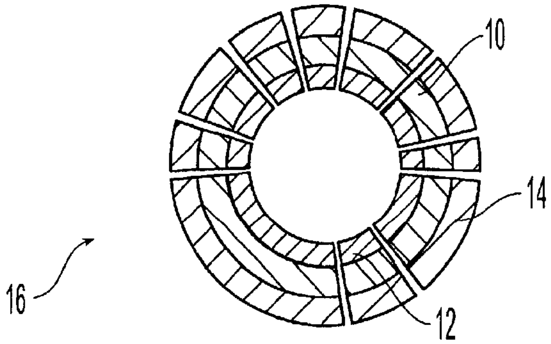

Fig. 1D

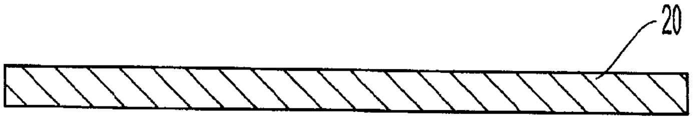

Fig. 2A

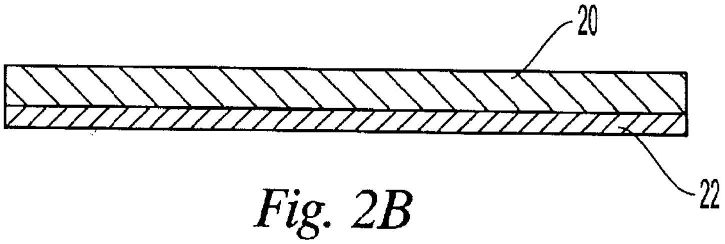

Fig. 2B

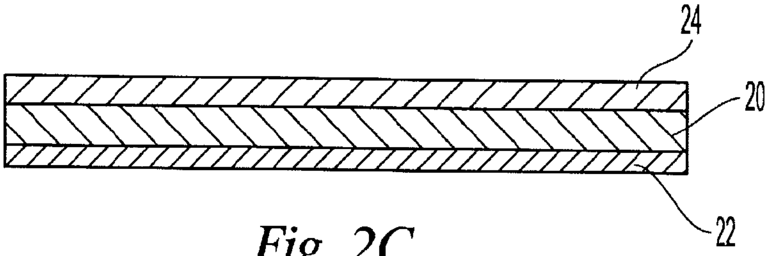

Fig. 2C

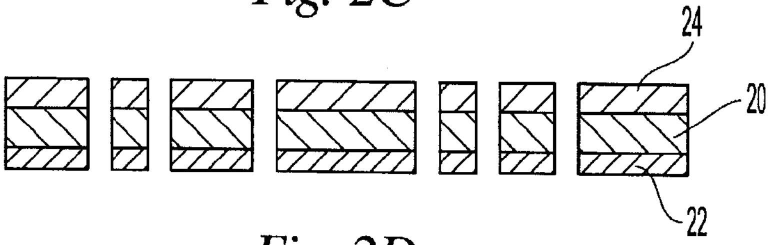

Fig. 2D

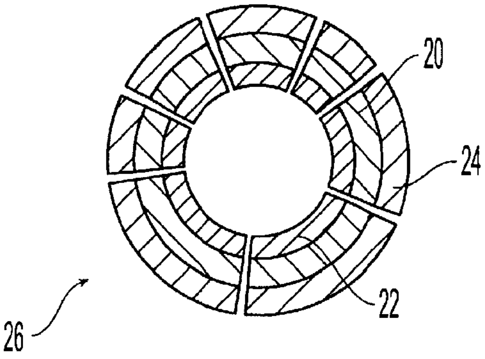

Fig. 2E

METHOD FOR MANUFACTURING A MEDICAL DEVICE HAVING A COATED PORTION BY LASER ABLATION

FIELD OF THE INVENTION

This invention relates generally to a method for manufacturing a medical device. More particularly, the invention is directed to a method for manufacturing a medical device having a coated portion by laser ablation.

BACKGROUND OF THE INVENTION

Implantable medical devices, such as prosthesis or stents, are used to reduce restenosis after balloon angioplasty or other procedures involving catheters. Usually, the suitable medical device or stent is cylindrical in shape. The walls of the cylindrical structure can be formed of metal or polymer with openings therein, e.g., a mesh. The stent is implanted into a body lumen, such as a blood vessel, where it stays permanently, to keep the vessel open and to improve blood flow to the heart muscle and relieve symptoms. Stents can also be positioned in other parts of the body, such as the kidneys or the brain. The stent procedure is fairly common, and various types of stents have been developed and actually used. However, since the bare metal surface of the stents may trigger restenosis, the stent surface should be altered to make it more biocompatible. Stents coated with polymers have been offered to reduce likelihood of restenosis caused by the metal surface of stents. Further, there are various types of polymer coats for stents which contain drugs which are delivered to an afflicted area of a body lumen. Drugs may be either bonded chemically, physically or absorbed in the polymer matrix. Also, for the purpose of obtaining drug delivery stents, the drugs may be directly coated or immobilized onto the stents, e.g. using a binding molecule between the drug molecule and the stent surface.

Previously, such coated stents have been manufactured by shaping the body of the stents first by photo-etching, laser ablation, electron beam ablation, or any other means, and then coating the stents with polymer compositions or drug compositions by dip-coating, spray-coating or any other means. However, due to the complex geometry of the stent, applying an even coating on a metal stent is very difficult. Therefore, methods for easily manufacturing a stent with uniform coating(s) are necessary.

In addition, the polymer coating, when applied by methods in the art, tends to create bridges at small gaps or corners between stent struts. Also, in the conventional methods, wherein a coating process takes place after a shaping process, it is almost impossible to selectively coat the stent. For example, it is impossible to coat one side of a stent without coating the other side or to apply different coatings to the outside and inside of a stent. Therefore, there is a need for methods of making a stent, especially coated stent, wherein the coating(s) does not form bridges at gaps or corners, and wherein selective coating of the stent can be readily achieved.

SUMMARY OF THE INVENTION

These and other objectives are accomplished by the present invention. To achieve the aforementioned objectives, a method has been invented for manufacturing a medical device having a coated portion by laser ablation.

An embodiment of the present invention is a method for manufacturing a medical device having a coated portion which comprises obtaining a structure having an inner surface and an outer surface. At least a portion of the inner or outer surface is coated with a first coating material. Then, the coated structure is ablated with a laser to form at least one opening therein to form the coated portion.

In another embodiment of the present invention, the method for manufacturing a medical device having a coated portion comprises obtaining a plate having a first surface and a second surface. At least a portion of the first surface or second surface is coated with a first coating material. The coated plate is then ablated with a laser to form at least one opening in the coated plate. Afterward, the coated and ablated plate is formed by folding or shaping into the medical device.

DESCRIPTION OF THE FIGURES

FIGS. **1A** through **1D** show the steps of an embodiment of the present invention.

FIG. 1A depicts a cross-sectional view of a tubular structure.

FIG. 1B depicts a cross-sectional view of the tubular structure after a coating is applied on its inner surface.

FIG. 1C depicts a cross-sectional view of the tubular structure after another coating is applied on its outer surface.

FIG. **1D** depicts a cross-sectional view of a coated tube-like portion of a medical device formed by ablating the tubular structure with a laser.

FIGS. **2A** through **2E** show steps of another embodiment of the present invention.

FIG. 2A depicts a cross-sectional view of a plate.

FIG. 2B depicts a cross-sectional view of the plate after a coating is applied on its first surface.

FIG. 2C depicts a cross-sectional view of the plate after another coating is applied on its second surface.

FIG. 2D depicts a cross-sectional view of the coated plate after laser ablation.

FIG. 2E depicts a cross-sectional view of a coated tube-like portion of a medical device made by forming the ablated plate into a desired shape.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In a method of the present invention, a structure or a plate is coated first, and then, ablated by a laser to form openings. Such ablation may be conducted with a ultrashort-pulse laser. "Ultrashort-pulse lasers" refer to lasers (light amplification by stimulated emission of radiation) consisting of pulses with durations shorter than about 10 pico ($=10^{-11}$) second. The ultrashort-pulse laser is clearly distinguished from conventional continuous wave and long-pulse lasers (nanosecond (10^{-9} sec) laser) which have significantly longer pulses.

When a material is ablated by a conventional laser, the material is removed by thermal ablation wherein the material is locally heated to near melting point or boiling point. Thus, ablation using conventional lasers has various problems. For example, the ablation is furthermore accompanied by a heat transfer and a strong thermal shock to surrounding material which might cause serious damage, such as cracking. Also, the material once removed tends to redeposit or re-solidify on the surrounding surface. Thus, a material ablated by a conventional laser must be cleaned to remove the redeposited material surrounding the cut surface. Hence, if a material having an immobilized molecule on its surface is ablated by a conventional laser, because a clearing step is required, the immobilized molecule may be washed away at the cleaning step. Also, since process parameters for a conventional laser ablation, such as boiling point and absorption of the laser light, varies according to materials to be ablated, a layered material consisting of layers made of different materials cannot be ablated by a conventional laser.

On the other hand, ablation using an ultrashort-pulse laser is free from such problems. The ultrashort-pulse deposits its energy so quickly that it does not interact at all with the plume of vaporized material, which would distort and bend the incoming beam and produce a rough-edged cut. The plasma plume leaves the surface very rapidly, ensuring that it is well beyond the cut edges before the arrival of the next laser pulse. Since the pulse is very short, atoms in a material to be ablated are stationary in space with respect to the pulse duration. As a result, the ultrashort-pulse laser does not react differently between dielectric materials and electric materials. Thus, any material, including glasses, polymers, ceramics, silicon, and metals, can be ablated with very high precision without damage in surrounding area by ultrashort-pulse lasers due to the absence of heat shock waves. In addition, the surface ablated with a ultrashort-pulse laser has an excellent quality which does not need further polishing as required for a surface ablated with a conventional laser because redeposition is less or absent.

The lasers suitable for use in the method of the present invention are preferably ultrashort-pulse lasers consisting of pulses shorter than about 10^{-11} second, preferably shorter than about 10^{-12} second, and most preferably shorter than about 10^{-13} second which are referred to as femtosecond lasers. The ultrashort-pulse laser used for the

The intensity (fluence) of the laser radiation that is required to ablate a material is dependent on the material to be ablated. Specifically each material has its own laser-induced optical breakdown (LIOB) threshold which characterizes the fluence required to ablate the material at a particular pulse width. Also the fluence of the ultrashort-pulse laser suitable for the present invention can be chosen according to the thickness of the tube wall, the thickness of the coating and each material. Furthermore, the number of pulses needed to ablate completely through a material can be calculated for a given energy or fluence.

For example, a hole without any redeposition can be drilled into a 0.7 mm-thick stainless steel plate coated with a 0.3 mm-thick poly(ethylene terephthalate) coating on its one surface, using a laser with a pulse duration of 220 femtosecond and a fluence of 0.6 J/cm^2 at a wavelength of 780 nm with a repetition rate of 1 kHz commercial femtosecond Ti:sapphire laser and amplifier system (SPECTRA-PHYSICS, SPITFIRE). As another example, a hole without any redeposition can be drilled into a 0.7 mm-thick piece of tantalum with a 0.3 mm-thick poly(ethylene oxide)/poly (butylene terephthalate) copolymer coating using a laser with a pulse duration of 120 femtosecond and a fluence of 0.5 J/cm^2 with the same system used above.

The laser ablation of the present invention can be conducted using any additional techniques for improved accuracy and efficiency of such ultrashort-pulse laser ablation, e.g. diffractive optical elements (DOEs) and/or polarization trepanning. See C. Momma et al., *Beam delivery offemtosecond laser radiation by diffractive optical elements*, Appl. Phys. A 67, 517–520 (1998); S. Nolte et al., *Polarization effects in ultrashort-pulse laser drilling*, Appl. Phys. A 68, 563–567 (1999), both are incorporated herein by reference.

The ultrashort-pulse-lasers-are known to artisans. For example, they are thoroughly disclosed by M. D. Perry et al.

in *Ultrashort-Pulse Laser Machining, Section* K-ICALEO 1998, pp.1–20, which is incorporated herein by reference.

An embodiment of the present invention is illustrated in FIGS. **1A–1D** in which a tubular structure made of a suitable medical device material is coated with a coating material or composition. FIG. **1A** depicts a cross-sectional view of a tubular structure **10** made of a suitable medical device material. The inner surface of the tubular structure **10** is coated with first coating material or composition **12** (FIG. **1B**). Then, the outer surface of the tubular structure **10** is also coated with second coating material or composition **14** (FIG. **1C**) which can be the same as the first coating material or composition. The tubular structure **10** having an inner coating **12** and outer coating **14** is ablated by an ultrashort-pulse laser to form openings that made up a geometric pattern in the tubular structure (FIG. **1D**). In this manner, a coated tube-like portion of a medical device **16** is formed. Alternatively, only one of the surfaces, e.g. inner or outer, may be coated.

Another embodiment is illustrated in FIGS. **2A–2E**. FIG. **2A** depicts a cross-sectional view of a plate **20** made of a suitable medical device material. A first surface of the plate **20** is coated with first coating material or composition **22** (FIG. **2B**). Then, the second surface of the plate **20** is also coated with second coating material or composition **24**, which can be the same as the first coating material or composition (FIG. **2C**). The plate **20** having first coating **22** and second coating **24** is ablated by an ultrashort-pulse laser to form openings that make up a geometric pattern (FIG. **2D**). The plate is then folded into a desired shape to form a coated tube-like portion of a medical device **26**.

The term "structure" used in relation to a medical device means any structure which is at least a part of a medical device, such as a tubular structure. Likewise, the term "coated portion" used in relation to a medical device means any portion of a medical device which has (a) coating(s) on its surface(s). An example of such coated portion is a coated tube-like portion. Medical devices that can be fabricated by the method of the present invention includes those that include a tube-like or cylindrical-like portion. The tube-like portion of the medical device need not to be completely cylindrical. For instance, the cross-section of the tube-like portion can be any shape, such as rectangle, a triangle, etc., not just a circle. Such devices include, without limitation, stents and grafts. A bifurcated stent is also included among the medical devices which can be fabricated by the method of the present invention.

Preferably, the medical device is a stent. Stents suitable for the present invention include vascular stents such as self-expanding stents and balloon expandable stents. Examples of self-expanding stents are illustrated in U.S. Pat. Nos. 4,655,771 and 4,954,126 issued to Wallsten and 5,061,275 issued to Wallsten et al. Examples of appropriate balloon-expandable stents are shown in U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco and U.S. Pat. No. 4,886,062 issued to Wiktor.

Appropriate materials for making the medical device are not limited for the present invention, and any material including ceramics, polymers and metals can be used for manufacturing the device by the method of the present invention. Preferably, the device is made of a biocompatible material. Examples for such polymers include poly(ethylene terephthalate), polyacetal, poly(lactic acid), poly(ethylene oxide)/poly(butylene terephthalate) copolymer, and polycarbonate. Examples for such metals include titanium, stainless steel, platinum, tantalum or gold/platinum alloy.

In the present invention, the term "coating" encompasses all ways of coating, such as using plasma, dipping, spraying, etching, covering, plating, co-extruding and all modern chemical ways of attaching bio-molecules to surfaces as well as conventional coating. The surface is coated with a material by a method known to the artisans, such as dipping into a polymer, spraying a coating composition onto the surface, or attaching bio-molecules to surfaces. The surface of the structure or plate is optionally subjected to a pre-treatment, such as roughing, oxidizing or adding a primer, and then coated. Adding a primer is preferable as such pre-treatment. In another embodiment, the structure or plate can be covered with a film. Further, in another embodiment, the structure or plate can be made by co-extrusion of the medical device material and the coating material. More than one coating method can be used to make a medical device. Thickness of coatings can range from almost a single layer of molecules to about 0.1 mm. Suitable thickness as of the coating are known in the art and can be selected by artisans.

Medical devices coating materials suitable for the present invention include any coating material for the stent which are known to the skilled artisan. Suitable coating materials include, without limitation, metals, such as tantalum, stainless steel, nitinol, titanium, and alloys, polymeric materials, such as poly-L-lactic acid, polycarbonate, polyethylene terephtalate, silicones, polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, hydrogels and EPDM rubbers. Such coatings include biologically active molecules, such as heparine or insuline molecules, directly attached to oxide molecules on the surface of the structure as explained below.

Also, the coating can be a drug-releasing coating which immediately or gradually releases a biologically active material. Coating polymer useful for drug coating includes hydrogel polymers which are often used to contain the biologically active material and are disclosed in U.S. Pat. No. 5,304,121, U.S. Pat. No. 5,464,650, PCT publication WO95/03083 and U.S. Pat. No. 5,120,322, which are incorporated by reference. However, a non-hydrogel can be also used. Although polymeric molecules can be combined with biologically active molecules, biologically active materials can be directly immobilized on the surface. As disclosed in U.S. Pat. No. 5,356,433 to Rowland et al., polysaccharides can be immobilized to metallic surfaces by applying an organosilane coating with amine functionality and then applying a polysaccharide using carbodlimide as a coupling gent. U.S. Pat. No. 5,336,518 to Narayanan et al. also discloses that a polysaccharide can be immobilized on a surface by applying a coat of heptafluorobutylmethacrylate (HFBMA) by radiofrequency (RF) plasma deposition, creating functional groups on the surface by RF plasma with water vapor, and then applying the polysaccharide using carbodiimide. Moreover, examples of medical devices, in particular, stents coated with polymer/biologically active material coatings are described in U.S. Pat. No. 5,879,697 which is incorporated herein by reference.

The term "biologically active material" encompasses therapeutic agents, such as drugs, and also genetic materials and biological materials. The genetic materials mean DNA or RNA, including, without limitation, of DNA/RNA encoding a useful protein stated below, intended to be inserted into a human body including viral vectors and non-viral vectors. Viral vectors include adenoviruses, gutted adenoviruses, adeno-associated virus, retroviruses, alpha virus (Semliki Forest, Sindbis, etc.), lentiviruses, herpes simplex virus, ex vivo modified cells (e.g., stem cells, fibroblasts, myoblasts, satellite cells, pericytes, cardiomyocytes, sketetal myocytes, macrophage), replication competent viruses (e.g., ONYX-015), and hybrid vectors. Non-viral vectors include artificial chromosomes and mini-chromosomes, plasmid DNA vectors (e.g., pCOR), cationic polymers (e.g., polyethyleneimine, polyethyleneimine (PEI)) graft copolymers (e.g., polyether-PEI and polyethylene oxide-PEI), neutral polymers PVP, SP1017 (SUPRATEK), lipids or lipoplexes, nanoparticles and microparticles with and without targeting sequences such as the protein transduction domain (PTD). The biological materials include cells, yeasts, bacteria, proteins, peptides, cytokines and hormones. Examples for peptides and proteins include growth factors (FGF, FGF-1, FGF-2, VEGF, Endotherial Mitogenic Growth Factors, and epidermal growth factors, transforming growth factor α and β, platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor), transcription factors, proteinkinases, CD inhibitors, thymidine kinase, and bone morphogenic proteins (BMP's), such as BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8. BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Cells can be of human origin (autologous or allogeneic) or from an animal source (xenogeneic), genetically engineered, if desired, to deliver proteins of interest at the transplant site. The delivery media can be formulated as needed to maintain cell function and viability. Cells include whole bone marrow, bone marrow derived mono-nuclear cells, progenitor cells (e.g., endothelial progentitor cells) stem cells (e.g., mesenchymal, hematopoietic, neuronal), pluripotent stem cells, fibroblasts, macrophage, and satellite cells.

Biologically active material also includes non-genetic therapeutic agents, such as:

anti-thrombogenic agents such as heparin, heparin dervatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone);

anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid, amlodipine and doxazosin;

anti-inflammatory agents such as glucocorticoids, betamethasone, dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine;

antineoplastic/antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, methotrexate, azathioprine, adriamycin and mutamycin; endostatin, angiostatin and thymidine kinase inhibitors, taxol and its analogs or derivatives;

anesthetic agents such as lidocaine, bupivacaine, and ropivacaine;

anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin (aspirin is also classified as an analgesic, antipyretic and anti-inflammatory drug), dipyridamole, protamine, hirudin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides;

vascular cell growth promotors such as growth factors, Vascular Endothelial Growth Factors (FEGF, all types including VEGF-2), growth factor receptors, transcriptional activators, and translational promotors;

vascular cell growth inhibitors such as antiproliferative agents, growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin;

cholesterol-lowering agents; vasodilating agents; and agents which interfere with endogenous vasoactive mechanisms;

anti-oxidants, such as probucol;

antibiotic agents, such as penicillin, cefoxitin, oxacillin, tobranycin

angiogenic substances, such as acidic and basic fibrobrast growth factors, estrogen including estradiol (E2), estriol (E3) and 17-Beta Estradiol; and

drugs for heart failure, such as digoxin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors including captopril and enalopril.

In the devices made by the method of the invention, both surfaces of the tube-like portion can be coated with a same material at the same time.

Also, one surface of the structure or plate need not be coated, while the other surface has a coating. A medical device having such portion is preferable for a drug-delivery medical device for delivering a biologically active material to a blood vessel surface while minimizing the amount of biologically active material which is delivered into the blood stream. Such a medical device is also preferable when the coating is easily damaged during implantation of the medical device, e.g., because of the unfolding shear-action of the delivery balloon.

Further in another embodiment, inner and outer surfaces of the portion of the medical device can be coated with different materials. For example, a stent can have a polymer coating having an anti-thrombogenic agent on the inner surface which directly contacts blood flow and a polymer coating having an anti-inflammatory agent on the outer surface which directly contacts blood vessel wall. The inner surface and the outer surface can be coated by the different methods. Also, there can be more than one coating on a surface. Furthermore, an entire surface of the medical device is not necessarily coated.

In the present invention, the coated structure or plate is ablated by a laser to form openings. The openings along with the remaining parts of the structure or plate make up the geometric pattern structure of the medical device. The structure or plate can be moved while the laser is held stationary to ablate the structure or plate into pattern, or alternatively, the laser can be programmed to move along a predetermined pattern by a method known to artisans. A combination of both, i.e. moving both the laser and the structure or plate, is also possible. In the present invention, even a coated stent having a complex stent pattern can be made with high precision. A medical devices having multiple coating layers and a complicated geometry pattern can also be easily manufactured by the method of the present invention without flaws such as polymer-bridges at gaps or corners. Also, the layer thickness can be easily controlled by the method of the present invention.

In the case where a plate is coated and ablated, the plate is formed into a portion of the medical device in the way known to artisans. In case the coated portion is a tube-like portion, it is formed by forming the flat plate into a tube-like shape and attaching the opposing edges of the plate together such as by fusing the two opposing sides. A method of fusing appropriate to a stent material can be chosen. Methods of fusing include fusing by heat or using adhesive.

After the ablation of the present invention, there is no need to polish the ablated medical device to avoid rough cut surface because of the high quality of the cut surface.

Furthermore, a plurality of medical devices can be manufactured by coating one large structure and, as ablating it as explained above, cutting the structure into individual coated portions. For example, if the coated portion is a tube-like portion, a long tubular structure is coated first, and then ablated, and then cut into individual tube-like portions of medical devices. Likewise, a large plate can be coated first, cut into a smaller plate, and then formed into an individual coated structure and ablated. Alternatively, a large coated plate can be shaped into a large coated structure, and then it is cut into individual coated structures as ablated. In this way, a plurality of medical devices be made by using one coating step. Also, all of the medical devices will have uniform coating thicknesses.

If necessary, the thickness of the coating can be easily measured before the ablation step. For example, it is very useful to know an amount of a biologically active material contained in a medical material. This amount can be calculated in the present invention by measuring the thickness of the coating after the coating is placed on the medical device. For example, based on the concentration of biologically active material in the coating composition, the thickness of the coating, the amount of biologically active material placed on the device can be determined.

The description contained herein is for purposes of illustration and not for purposes of limitation. Changes and modifications may be made to the embodiments of the description and still be within the scope of the invention. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety, for all purposes related to this disclosure.

I claim:

1. A method for manufacturing a coated medical device having a coated portion having at least one opening therein, wherein the method comprises the steps of:

(a) obtaining a metal structure having an inner surface and an outer surface;

(b) coating at least a portion of the inner or outer surface of the structure with a first non-metallic coating material to form a coated structure; and

(c) simultaneously ablating through the coating material and structure of the coated structure with an ultrashort-pulse laser to form at least one opening therein.

2. The method of claim 1, wherein the structure is a tubular structure.

3. The method of claim 1, wherein the medical device is a stent.

4. The method of claim 1, wherein step (b) comprises only coating the inner surface of the structure with the first coating material.

5. The method of claim 1, wherein step (b) comprises only coating the outer surface of the structure with the first coating material.

6. The method of claim 1, wherein step (b) comprises:

(i) coating the inner surface of the structure with the first coating material and

(ii) coating the outer surface of the structure with a second non-metallic coating material.

7. The method of claim **6**, wherein the first coating material and the second coating material are the same.

8. The method of claim **1**, wherein the first coating material is a coating composition and the surface is coated by dipping the surface into the coating composition.

9. The method of claim **1**, wherein the first coating material is a coating composition and the surface is coated by spray-coating the coating composition onto the surface.

10. The method of claim **1**, wherein the first coating material comprises a polymer and a biologically active material.

11. The method of claim **1**, wherein the first coating material comprises a biologically active material, and the coating step (b) is conducted by immobilizing the first coating material onto at least a portion of the surface.

12. The method of claim **1**, wherein the coated structure is ablated to form a plurality of openings therein that define a plurality of struts.

13. The method of claim **1**, which further comprises cutting the coated structure into sections to form more than one coated portion.

14. The method of claim **13**, wherein the cutting step is conducted between coating step and the ablating step.

15. A method for manufacturing a coated medical device having a coated portion having at least one opening therein, wherein the method comprises the steps of:

(a) obtaining a metal plate having a first surface and a second surface;

(b) coating at least a portion of the first surface or second surface with a first non-metallic coating material to form a coated plate;

(c) simultaneously ablating through the coating material and plate of the coated plate with an ultrashort-pulse laser to form at least one opening therein; and

(d) forming the coated plate into a tubular medical device.

16. The method of claim **15**, which further comprises forming a tubular structure from the coated and ablated plate obtained in step (c).

17. The method of claim **15**, wherein the medical device is a stent.

18. The method of claim **15**, wherein step (b) comprises only coating the first surface of the plate with the first coating material.

19. The method of claim **15**, wherein step (b) comprises only coating the second surface of the plate with the first coating material.

20. The method of claim **15**, wherein step (b) comprises:

(i) coating the first surface of the plate with the first coating material and

(ii) coating the second surface of the plate with a second non-metallic coating material.

21. The method of claim **15**, wherein the first coating material and the second coating material are the same.

22. The method of claim **15**, wherein the first coating material is a coating composition and the surface is coated by dipping the surface into the coating composition.

23. The method of claim **15**, wherein the first coating material is a coating composition and the surface is coated by spray-coating the coating composition onto the surface.

24. The method of claim **15**, wherein the first coating material comprises a biologically active material, and coating is conducted by immobilizing the first coating material onto at least of a portion of the surface.

25. The method of claim **15**, wherein the first coating material comprises a polymer and a biologically active material.

26. The method of claim **15**, wherein the coated plate is ablated to form a plurality of openings therein that define a plurality of struts.

27. The method of claim **15**, which further comprises cutting the coated plate into sections and forming more than one coated and ablated tubular structure.

28. The method of claim **27**, wherein the cutting step is conducted between the coating step and the ablating step.

29. The method of claim **27**, wherein the coated plate is cut as it is ablated.

30. A method for manufacturing a coated medical device having a coated portion having at least one opening therein, wherein the method comprises the steps of:

(a) obtaining a metal structure having an inner surface and an outer surface;

(b) coating at least a portion of the inner or outer surface of the structure with a first non-metallic coating material to form a coated structure; and

(c) simultaneously ablating through the coating material and structure of the coated structure with a laser to form at least one opening therein.

31. A method for manufacturing a coated medical device having a coated portion having at least one opening therein, wherein the method comprises the steps of:

(a) obtaining a metal plate having a first surface and a second surface;

(b) coating at least a portion of the first surface or second surface of the plate with a first non-metallic coating material to form a coated plate;

(c) simultaneously ablating through the coating material and plate of the coated plate with a laser to form at least one opening therein; and

(d) forming the coated plate into a tubular medical device.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,517,888 B1
DATED : February 11, 2003
INVENTOR(S) : Weber

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75], the residence of the inventor, "**Jan Weber**", should be -- Maple Grove, Minnesota. --

Signed and Sealed this

Twenty-ninth Day of July, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US005897911A

United States Patent [19]

Loeffler

[11] **Patent Number: 5,897,911**

[45] **Date of Patent: Apr. 27, 1999**

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[54] **POLYMER-COATED STENT STRUCTURE**

[75] Inventor: **Joseph P. Loeffler**, Mountain View, Calif.

[73] Assignee: **Advanced Cardiovascular Systems, Inc.**, Santa Clara, Calif.

[21] Appl. No.: **08/909,399**

[22] Filed: **Aug. 11, 1997**

[51] **Int. Cl.**^{6} **B05D 3/12**; B05D 7/22

[52] **U.S. Cl.** **427/2.25**; 427/2.3; 427/2.28

[58] **Field of Search** 427/2.3, 2.24, 427/2.25, 2.28, 358

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Primary Examiner—Diana Dudash
Attorney, Agent, or Firm—Fulwider Patton Lee & Utecht, LLP

[57] **ABSTRACT**

The thickness of a polymer coating applied to the interior surface of a stent is precisely controlled by fitting a mandrel within its interior. Fitment of an exterior mold serves to additionally control the thickness of polymer on the exterior surface of the stent. Alternatively, a preformed sheath of polymer is fitted to the interior of the stent whereby the subsequent application of polymer not only causes the exterior to become coated but also causes the sheath to become adhered to the stent.

21 Claims, 1 Drawing Sheet

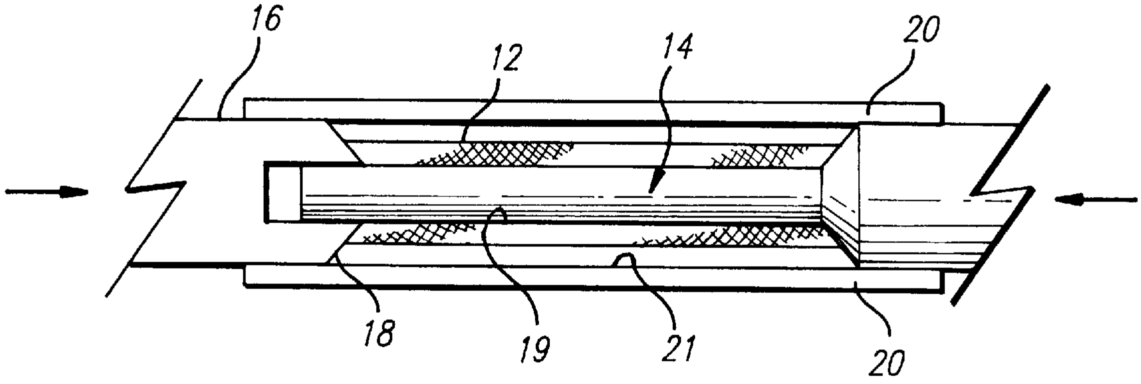


FIG. 1

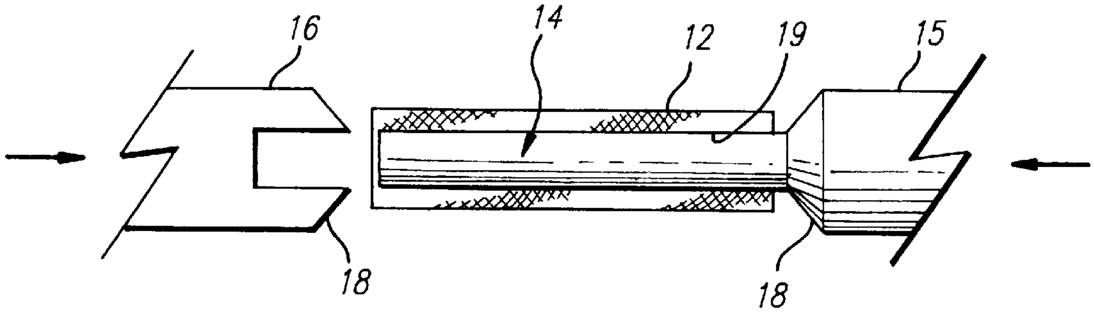


FIG. 2

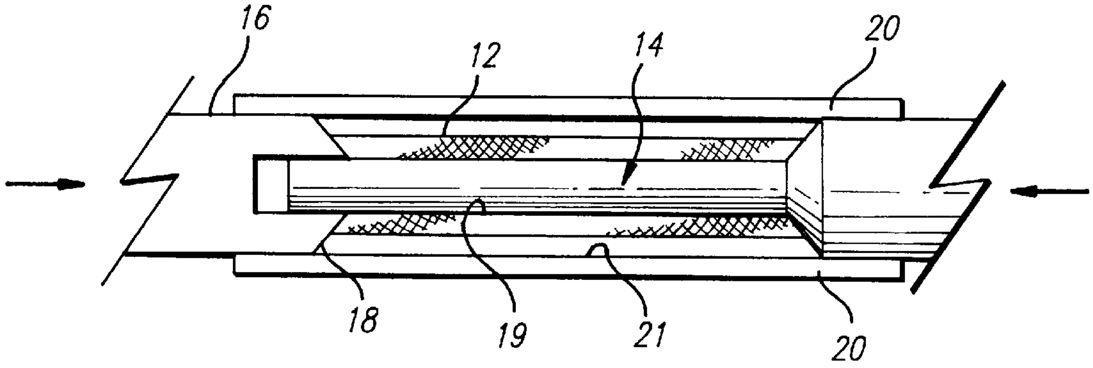
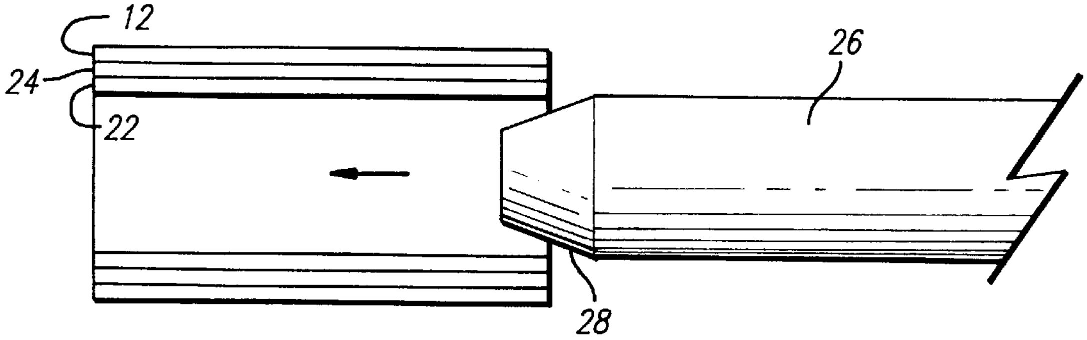


FIG. 3



POLYMER-COATED STENT STRUCTURE

BACKGROUND OF THE INVENTION

This invention relates generally to expandable intraluminal vascular grafts, commonly referred to as stents, and more particularly concerns the coating of metal stents with polymer materials capable of carrying and releasing therapeutic drugs.

Stents are implanted within vessels in an effort to maintain the patency thereof by preventing collapse and/or by impeding restenosis. Implantation of a stent is typically accomplished by mounting the stent on the expandable portion of a balloon catheter, maneuvering the catheter through the vasculature so as to position the stent at the desired location within the body lumen, and inflating the balloon to expand the stent so as to engage the lumen wall. The stent automatically locks into its expanded configuration allowing the balloon to be deflated and the catheter removed to complete the implantation procedure.

It is often desirable to provide localized pharmacological treatment of a vessel at the site being supported by the stent and it has been found convenient to utilize the stent as a delivery vehicle for such purpose. However, because of the mechanical strength that is required to properly support vessel walls, stents must typically be constructed of metallic materials which are not capable of carrying and releasing drugs. Various polymers on the other hand are quite capable of carrying and releasing drugs but generally do not have the requisite mechanical strength. A previously devised solution to such dilemma has been the coating of a stent's metallic structure with a polymer material in order to provide a stent capable of both supporting adequate mechanical loads as well as delivering drugs.

Various approaches have previously been used to join polymers to metallic stents including dipping, spraying and conforming processes. However, such methods have failed to provide an economically viable method of applying a very even coating of polymer on the stent surfaces or the ability to economically apply different thicknesses or different polymers in different areas on the same stent.

The prior art has been unable to overcome such shortcomings and a new approach is needed for effectively and economically applying a polymeric material to a metallic stent with a high degree of precision.

SUMMARY OF THE INVENTION

The present invention provides a method of joining a polymeric material with a metallic stent that overcomes the disadvantages and shortcomings of previously employed processes. More particularly, by such method, very precisely controlled thicknesses of polymer can be applied to selected surfaces of a stent. The resulting stent has the mechanical strength necessary to properly support a blood vessel while being capable of delivering a preselected quantity of drug or drugs over a desired period of time. Moreover, the attached polymer does not interfere in the deployment of the stent and therefore allows the stent to be freely expanded.

The methods of the present invention call for the use of mandrels and/or molds to apply precise amounts of polymer to the stent surfaces. Moreover, advantageous positioning of such implements relative to the stent allow the thickness of the polymer to be varied from surface to surface. It is thereby readily possible to apply a thicker layer of polymer to the blood-facing side of the stent than to the vessel-facing side or vice versa. Additionally, by employing successive molding operations, different polymers, selected for their differentiated ability to absorb and release different therapeutic agents, can be applied to selected surfaces of the stent. Alternatively, the polymer may be applied to one side of the stent as a preformed sheath, while the subsequent molding operation not only serves to coat the opposite surface of the stent but also serves to adhere the preformed sheath to the stent as well. Upon implantation of such stent with differentiated surfaces it is thereby possible to directly expose the vessel wall to one therapeutic agent while the blood is exposed to a different therapeutic agent. Alternatively, it is possible to load polymers with different carrying capacities of a particular therapeutic agent to thereby deliver different concentrations in a desired pattern.

The method of the present invention includes a number of alternative embodiments including the use of various combinations of mandrel configurations, and exterior molds. The polymer is applied by either a dip coating, pultrusion or injection molding process. The methods of the present invention ensure that very precisely dimensioned coatings result even after the drying and the cooling processes are completed. A final serration or separation step may be necessary for some stent configurations in order to restore the desired flexibility and expendability to the stent. A laser is used for such purpose to quickly and precisely cut and/or remove polymer from various locations on the coated stent.

These and other features and advantages of the present invention will become apparent from the following detailed description of a preferred embodiment which, taken in conjunction with the accompanying drawings, illustrates by way of example the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a cross-sectional view of a mandrel being positioned within a stent.

FIG. **2** is a cross-sectional view of a mandrel in position within a stent and an exterior mold positioned thereabout.

FIG. **3** is a cross-sectional view of a mandrel being inserted into a preformed sheath containing stent.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The figures generally illustrate the techniques used to apply polymer to a stent in accordance with the present invention. Any of a variety of stent configurations may be subjected to the coating process described herein including, but not limited to multi-link or slotted tube-type designs. The metals from which such stents are formed may include stainless steels, NiTi and tantalum among others. The polymer or a combination of polymers that are applied thereto are selected for their ability to carry and release, at a controlled rate, various therapeutic agents such as antithrombogenic or anti-proliferative drugs. The polymeric material of the invention preferably comprises a biodegradable, bioabsorbable polymeric film that is capable of being loaded with and capable of releasing therapeutic drugs. The polymeric materials preferably include, but are not limited to, polycaprolactone (PCL), poly-DL-lactic acid (DL-PLA) and poly-L-lactic acid (L-PLA) or lactide. Other biodegradable, bioabsorbable polymers such as polyorthoesters, polyiminocarbonates, aliphatic polycarbonates, and polyphosphazenes may also be suitable, and other non-degradable polymers capable of carrying and delivering therapeutic drugs may also be suitable. Examples of non-degradable synthetic polymers are Parylene®, Parylast® (from Advanced Surface Technology of Billerica, Mass.), polyurethane, polyethylene, polyethylene teraphthalate, ethylene vinyl acetate, silicone and polyethylene oxide (PEO).

Examples of therapeutic drugs, or agents that can be combined with the polymeric materials include antiplatelets, anticoagulants, antifibrins, antithrombins, and antiproliferatives. Examples of antiplatelets, anticoagulants, antifibrins, and antithrombins include but are not limited to sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of cytostatic or antiproliferative agents include angiopeptin (a somatostatin analogue from Ibsen), angiotensin converting enzyme inhibitors such as Captopril® (available from Squibb), Cilazapril® (available from Hoffman-LaRoche), or Lisinopril® (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, Lovastatin® (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), methotrexate, monoclonal antibodies (such as to PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available from Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic drugs or agents which may be appropriate include alpha-interferon and genetically engineered epithelial cells, for example.

While the foregoing therapeutic agents have been used to prevent or treat restenosis, they are provided by way of example and are not meant to be limiting, since other therapeutic drugs may be developed which are equally applicable for use with the present invention. The treatment of diseases using the above therapeutic agent are known in the art. Furthermore, the calculation of dosages, dosage rates and appropriate duration of treatment are previously known in the art.

FIG. **1** illustrates the method of the present invention in its simplest form. The stent **12** is first slipped onto a mandrel in the form of a core pin **14** after which a pin cap **16** is fitted to its distal end. The core pin extends from a proximal section **15** of increased diameter similar to the outer diameter of the pin cap. As these two pin components are advanced towards one another, the tapered configurations of the corresponding receiving surfaces **18** automatically cause the stent to become centered about the core pin. The interference fit between the core pin and pin cap ensures that the components remain assembled and properly aligned during subsequent handling and processing. The pin is precisely dimensioned to provide the desired spacing **19** between its exterior surface and the interior surface of the stent. Such fixation of the stent also serves to minimize the area of contact between the stent and mandrel, and is thereby limited to only two very narrow circles on the opposite edges of the stent.

The assembly is subsequently submersed in the selected polymer in its liquid or molten state. Adjustment of the viscosity of the polymer may be necessary in order to ensure free access to the space between the core pin and stent via the link spacings or slots. Such adjustment may be achieved either by thermal or chemical means and is best optimized by empirical methods as are well know in the art. The presence of the pin strictly limits and thereby precisely controls the maximum thickness of polymer that can be applied to the stent's interior surface. Moreover, prolonged or repeated contact with the polymer allows a substantially thicker layer of polymer to be built up on the exterior of the stent while the thickness of the interior layer remains constant. Alternatively, subsequent exposure to a second polymer allows the exterior, i.e. vessel side of the stent, to be coated with a different polymer than is attached to its interior, i.e. blood side. After the polymer or polymers have all solidified or sufficiently cured, the core pin and pin cap are removed.

As an alternative to the submersion or dipping technique, the core pin/stent assembly is fitted to the exit port of an extruder and the polymer is applied to the stent using a pultrusion technique well known in the art. Selection of the appropriate viscosity of the polymer is again critical not only to ensure perfusion of the polymer through openings in the stent and into the space between the stent and core pin but also to achieve adequate coverage.

FIG. **2** illustrates a further alternative embodiment of the present invention wherein an exterior mold is utilized in addition to the core pin described above. The stent **12** is again first mounted about the core pin **14** and pin cap **16** after which the entire assembly is fitted inside an external mold **20**. The stent is thereby secured in position so as to define a precise spacing between the exterior of the core pin and the interior surface of the stent **19** and between the exterior surface of the stent and the interior of the external mold **21**. Polymer is subsequently injected either via any number of routes including a passage extending through the core pin **14** or through the external mold **20**. The viscosity of the polymer must be selected to facilitate its flow into the mold and through the stent to ensure that an uninterrupted coating of the stent is achieved. Conditions that affect the viscosity requirements include but are not limited to the anticipated temperatures, cooling rates, molding time, orifice sizes, molding pressure, and the metal from which the stent is formed, etc. The appropriate viscosity is easily selected by one skilled in the art using simple empirical techniques. After the polymer has solidified or sufficiently cured, the coated stent and core pin are removed from the mold as a unit after which the core pin and pin cap are removed from the stent. Successive molding operations with differently sized core pins or outer molds allow layers of different materials to be built up on either the internal or exterior surface of the stent.

An alternative embodiment obviates the use of the core pin and cap described above whereby a preformed polymer sheath is initially inserted into the stent. By subsequently applying polymer in its liquid state to the exterior of the stent, such sheath becomes joined to the applied polymer and thus the stent becomes completely encased in polymer. The preformed nature of the sheath serves to precisely define the thickness of polymer applied to the interior surface of the stent. A dip coating process sans exterior mold allows the polymer to be selectively built up on the exterior side of the stent while the use of an external mold positively limits its external thickness. The polymer from which the sheath is preformed does not necessarily have to correspond to the polymer that is subsequently applied in its flowable form, thus disparate types of polymer can be applied to the surfaces of the stent.

FIG. **3** illustrates the preferred method of practicing this embodiment. The polymer sheath **24** that is to comprise the inner surface of the finished product is first applied to a teflon or silicon support tube **22**, either by dip coating or extrusion. The metal stent **12** is then slipped over such coated tube after which a tapered mandrel **26** is inserted thereunto. The taper **28** facilitates insertion and expands the polymer sheath snugly against the interior surface of the stent **12**. The exterior of the stent is then coated with polymer either by dipping or pultrusion sans mold or by injection molding with the use of an external mold. After curing, the mandrel **26** and support tube **22** are removed to provide a fully coated stent.

Depending upon the type of stent structure to which the polymer is applied, it may be necessary to remove some of the polymer or at least cut the polymer at selected sites in order to restore the requisite flexibility to the stent. A multi-link stent for example necessarily requires that the various links are able to undergo relative movement during the expansion of the devices. The presence of polymer or at least the presence of a continuous mass of polymer between such links could inhibit relative movement and thus inhibit expansion of the stent during deployment. In order to remedy such effect it is necessary to either remove or at the very least, perforate the polymer in such locations. The preferred method of doing so is with the use of a laser with which polymer material can be quickly and precisely penetrated as required.

With certain stent configurations, it is advantageous to apply polymer to the stent while such stent is in its expanded state. The stent is initially expanded, such as by advancing the core pin and pin cap towards on another to force the stent sufficiently high up along the tapered surface to achieve its deployed diameter. Alternatively, an oversized sheath and mandrel may be used. Any of the various alternative embodiments described above may then be utilized to apply the polymer. Application of the polymer while the certain stent configurations are expanded result in less webbing between the struts and yields greater final mechanical stability. Additionally, the final polymer coating may need little or no laser processing for separation or clean up before the stent is contracted down to its pre-delivery O.D.

After the stent is coated and trimmed, therapeutic agent or agents are loaded at desired concentration levels per methods well known in the art to render the device ready for implantation.

While a particular form of the invention has been illustrated and described, it will also be apparent to those skilled in the art that various modifications can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited except by the appended claims.

What is claimed is:

1. A method for coating a stent, comprising the steps of:

providing a stent having a generally cylindrical shape, said stent having an interior surface and an exterior surface;

securely positioning a mandrel within said stent to define a space of substantially constant thickness between said mandrel and said interior surface of said stent;

contacting said mandrel containing stent with a polymer in a flowable state;

allowing said polymer to transform to a substantially non-flowable state; and

removing said mandrel from said stent.

2. The method of claim **1**, wherein said mandrel containing stent is contacted with said polymer so as to coat said exterior surface of said stent with a layer of polymer having a thickness that is greater than the thickness of said space between said mandrel and the interior surface of said stent.

3. The method of claim **1** wherein said stent is contacted with said polymer by submerging said stent in a mass of said polymer in its flowable state.

4. The method of claim **1** wherein said stent is contacted with said polymer by a pultrusion technique.

5. The method of claim **1** further comprising the step of re-contacting said mandrel containing stent with said polymer in said flowable state after said polymer with which said stent had previously been contacted has transformed to said substantially non-flowable state and prior to removal of said mandrel whereby said exterior and interior surfaces of said stent become differentiated in terms of the thickness of the polymer coatings thereon.

6. The method of claim **1**, further comprising the step of contacting said stent with a second polymer in a flowable state after said first polymer has become transformed to a substantially non-flowable state and prior to removal of said mandrel whereby the exterior and interior surfaces of said stent become differentiated in terms of the polymers coated thereon.

7. The method of claim **1** wherein said mandrel comprises a core pin and pin cap, wherein said pin cap slidably receives the distal end of said core pin and wherein both said core pin and pin cap include a conical surface that extends to diameter greater than that of said stent, the method further comprising the step of advancing said pin cap along said core pin whereby the stent becomes coaxially secured in position relative to said core pin.

8. A method for coating a stent, comprising the steps of:

providing a stent having a generally cylindrical shape, said stent having an interior surface and an exterior surface;

securely positioning a mandrel within said stent to define a first space of a substantially constant first thickness between said mandrel and said interior surface of said stent;

securely positioning said mandrel containing stent within an exterior mold to define a second space of a substantially constant second thickness between said exterior mold and said exterior surface of said stent;

introducing a polymer in a flowable state into said first and second spaces;

allowing said polymer to transform to a substantially non-flowable state; and

removing said exterior mold from about said stent and said mandrel from within said stent.

9. The method of claim **8** and wherein said first thickness is greater than said second thickness.

10. The method of claim **9** wherein said second thickness is greater than said first thickness.

11. The method of claim **8** further comprising the steps of:

removing only said exterior mold from about said stent after said polymer has transformed into a substantially non-flowable state;

securely positioning said mandrel containing stent within a second exterior mold to define a third space between the exterior surface of said first polymer coated stent and said second exterior mold; and

introducing a second polymer in a flowable state into said third space.

12. A method of coating a stent, comprising the steps of:

providing a stent having a generally cylindrical shape, said stent having an interior surface and an exterior surface;

fitting a sheath preformed of a first polymer within said stent;

contacting said stent with a second polymer in a flowable state; and allowing said second polymer to transform into a substantially non-flowable state.

13. The method of claim **12** wherein said first and second polymers are the same.

14. The method of claim **12** wherein said first and second polymers are different.

15. The method of claim **12** further comprising the step of inserting a mandrel into said sheath of said first polymer fitted within said stent in order to expand said sheath of polymer against the interior surface of said stent.

16. The method of claim **15** where in said mandrel has a tapered tip.

17. The method of claim **12** further comprising the step of securely positioning said sheath containing stent within an exterior mold to define a space between the exterior surface of said stent and said mold having a constant first thickness.

18. The method of claim **17** where in said sheath of polymer has a constant second thickness and wherein said first and second thickness are equal.

19. The method of claim **17** wherein said cylinder of polymer has a constant second thickness and wherein said first and second thickness are not equal.

20. The method of claim **19** wherein said first thickness is greater than said second thickness.

21. The method of claim **19** wherein said second thickness is greater than said first thickness.

* * * * *

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(12) **United States Patent**
Harish et al.

(10) **Patent No.: US 6,506,437 B1**
(45) **Date of Patent: Jan. 14, 2003**

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(54) METHODS OF COATING AN IMPLANTABLE DEVICE HAVING DEPOTS FORMED IN A SURFACE THEREOF

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 54 days.

(21) Appl. No.: **09/690,907**

(22) Filed: **Oct. 17, 2000**

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(52) **U.S. Cl.** **427/2.25**; 623/1.34; 623/1.39; 623/1.42

(58) **Field of Search** 623/1.15, 1.34, 623/1.39, 1.42, 1.43, 1.45, 1.46; 427/2.14, 2.24, 2.25, 2.28, 2.1

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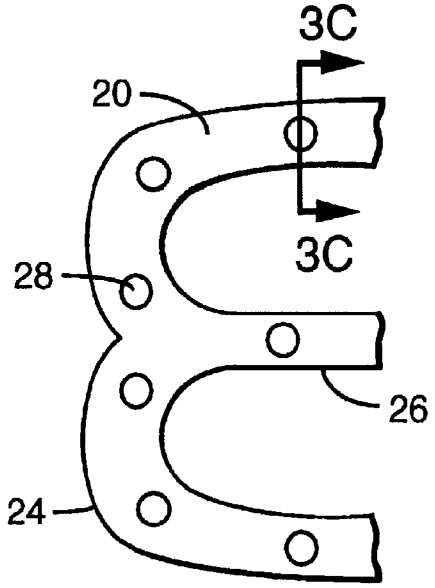
Primary Examiner—Paul B. Prebilic
Assistant Examiner—William H Matthews
(74) *Attorney, Agent, or Firm*—Squire Sanders & Dempsey L.L.P.

(57) ABSTRACT

The present invention provides methods of coating an implantable device, such as a stent or a graft, having a plurality of depots formed in a surface thereof. An exemplary method includes applying a composition including a polymer and a solvent to the implantable device proximate to the depots. Such application of the composition is performed at a first gas pressure. The method also includes applying a second gas pressure, which is greater than the first gas pressure, to the composition-coated device so that air pockets in the depots are eliminated, or at least reduced in size. The method also includes the act of removing the solvent from the composition to form a coating. An implantable device coated in accordance with the method is also provided.

The compositions employed in the methods may include one or more therapeutic substances such as antineoplastics, antimitotics, antiinflammatories, antiplatelets, anticoagulants, antifibrins, antithrombins, antiproliferatives, antibiotics, antioxidants, antiallergics, radioisotopes, and combinations thereof.

32 Claims, 6 Drawing Sheets



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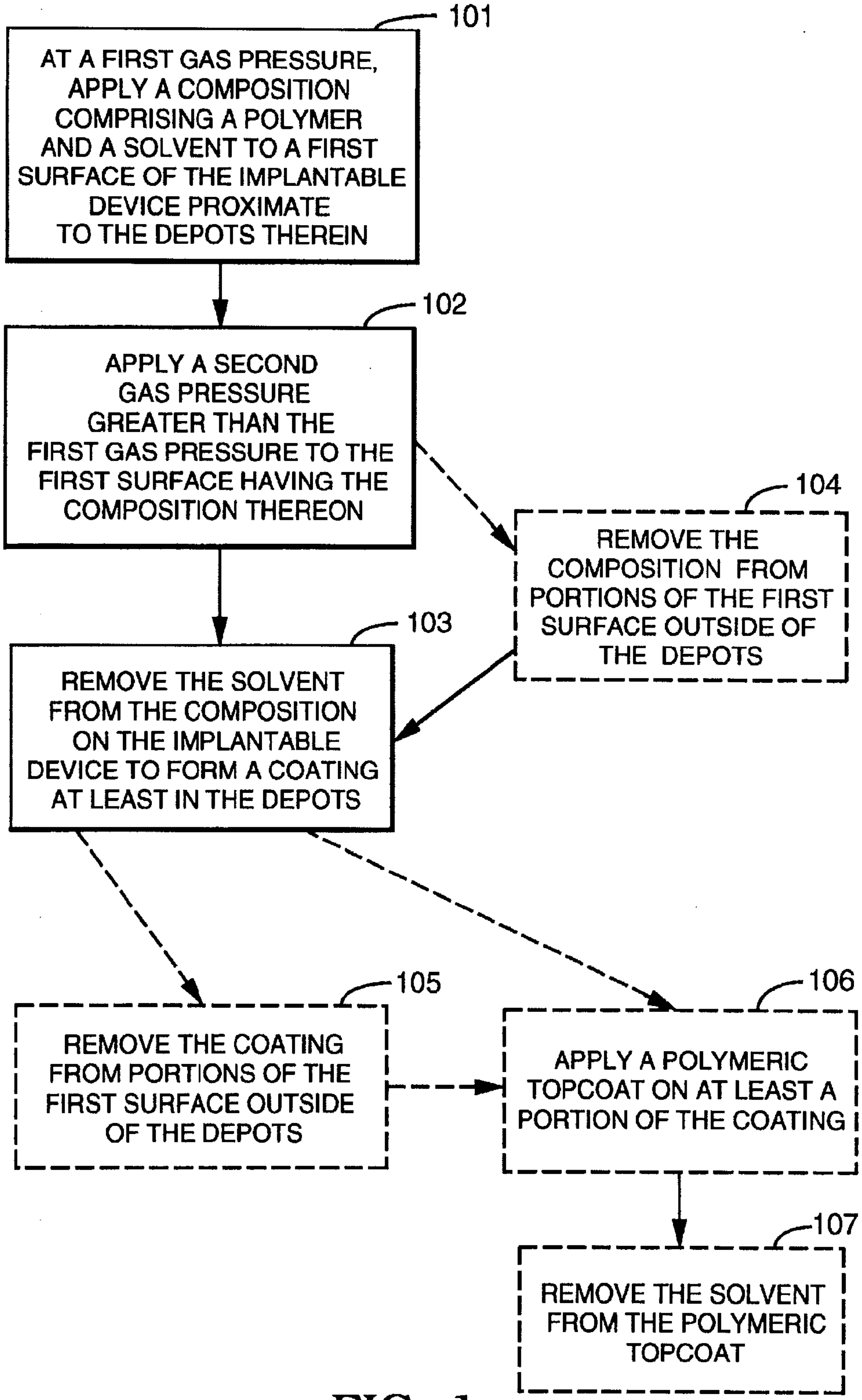
101
AT A FIRST GAS PRESSURE, APPLY A COMPOSITION COMPRISING A POLYMER AND A SOLVENT TO A FIRST SURFACE OF THE IMPLANTABLE DEVICE PROXIMATE TO THE DEPOTS THEREIN
102
APPLY A SECOND GAS PRESSURE GREATER THAN THE FIRST GAS PRESSURE TO THE FIRST SURFACE HAVING THE COMPOSITION THEREON
104
REMOVE THE COMPOSITION FROM PORTIONS OF THE FIRST SURFACE OUTSIDE OF THE DEPOTS
103
REMOVE THE SOLVENT FROM THE COMPOSITION ON THE IMPLANTABLE DEVICE TO FORM A COATING AT LEAST IN THE DEPOTS
105
REMOVE THE COATING FROM PORTIONS OF THE FIRST SURFACE OUTSIDE OF THE DEPOTS
106
APPLY A POLYMERIC TOPCOAT ON AT LEAST A PORTION OF THE COATING
107
REMOVE THE SOLVENT FROM THE POLYMERIC TOPCOAT

FIG. 1

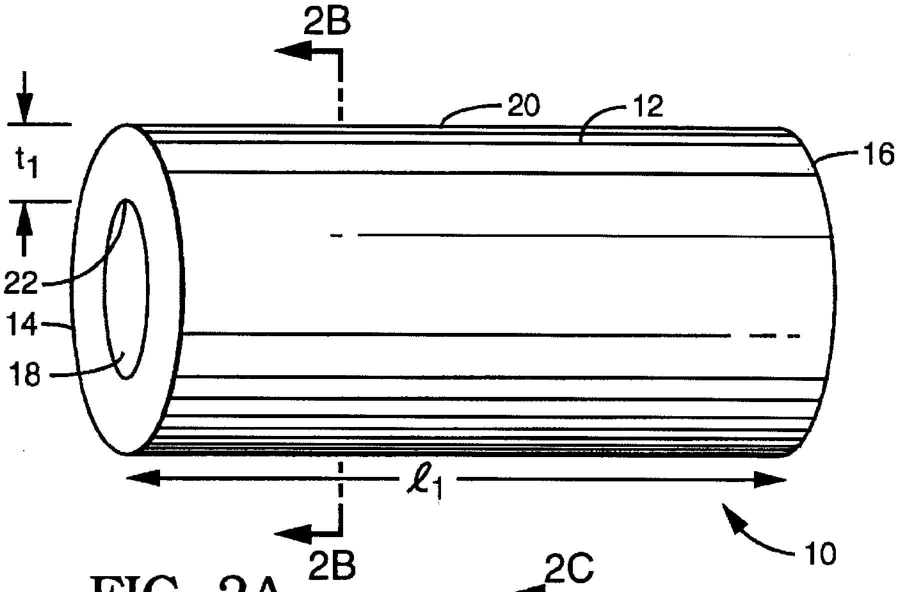

FIG. 2A

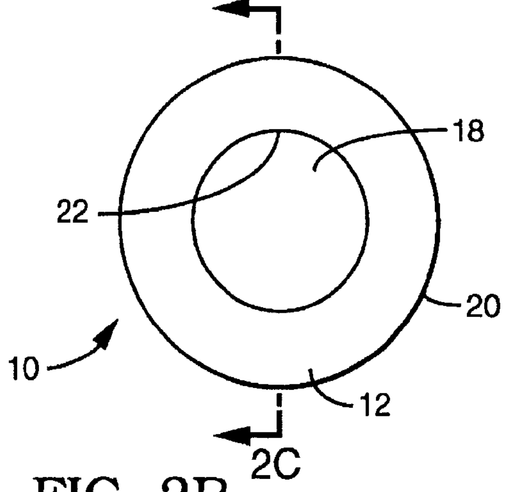

FIG. 2B

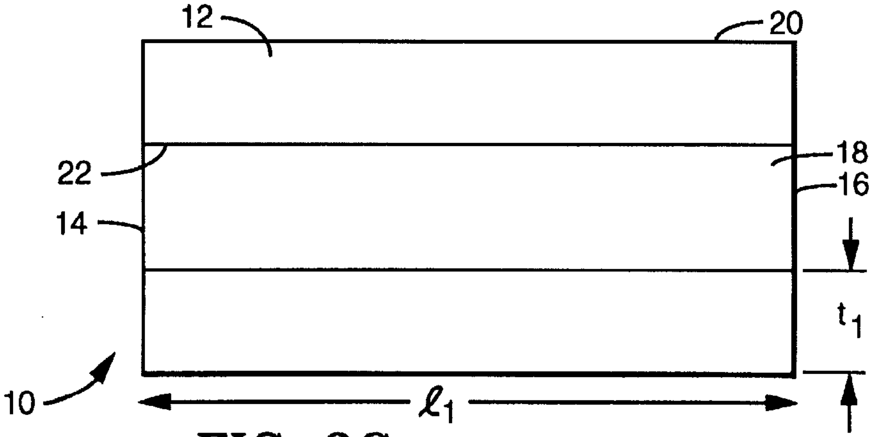

FIG. 2C

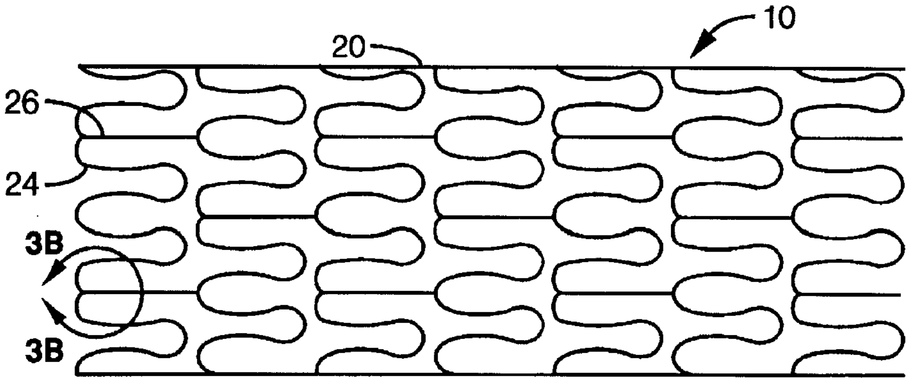

FIG. 3A

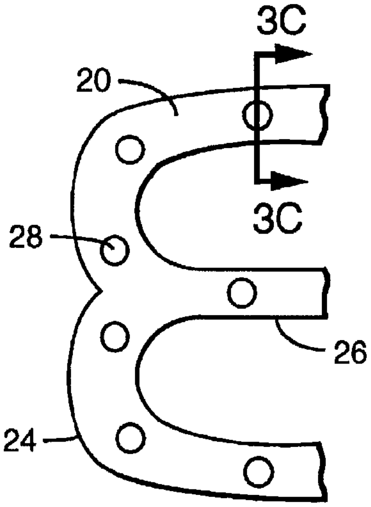

FIG. 3B

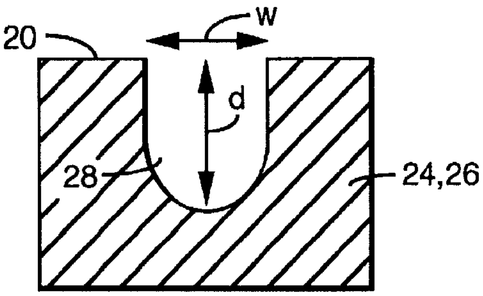

FIG. 3C

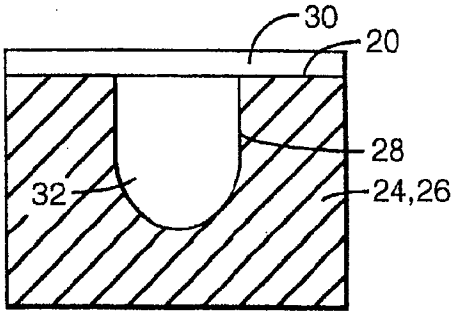

FIG. 4A

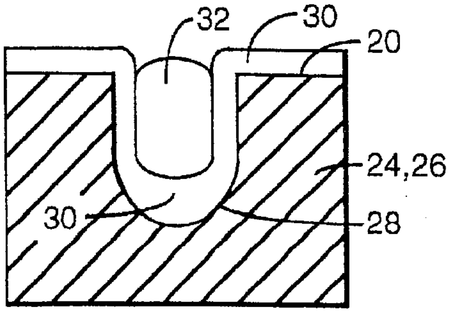

FIG. 4B

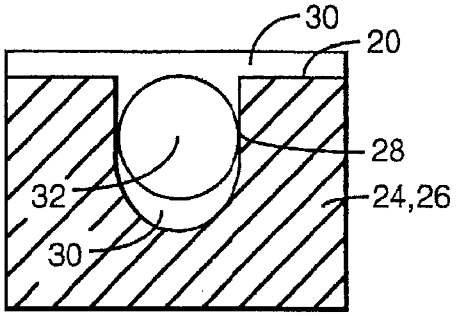

FIG. 4C

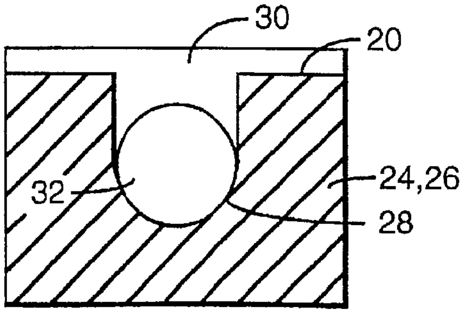

FIG. 4D

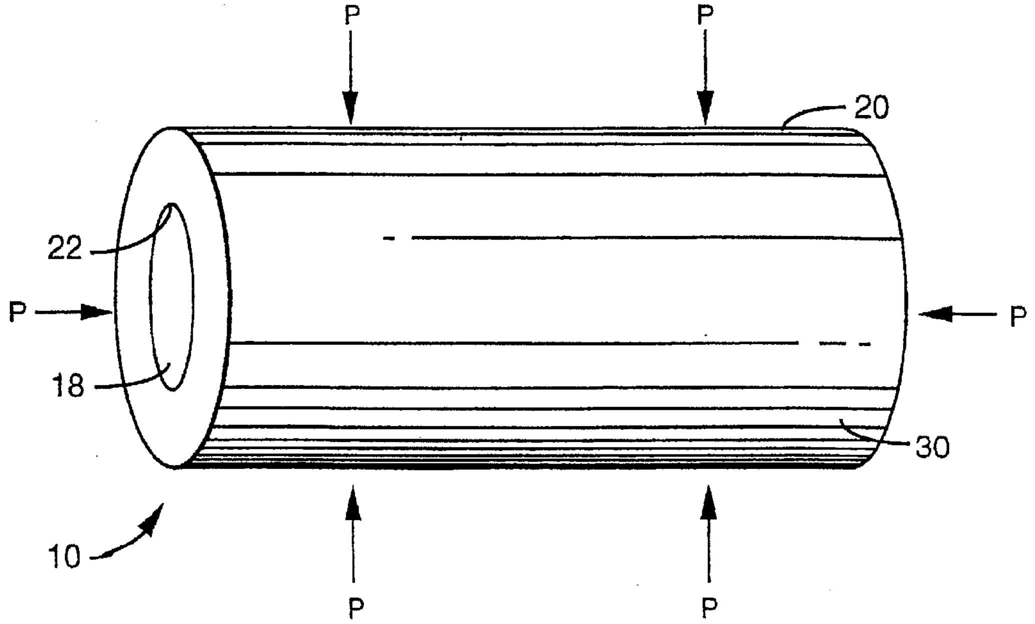

FIG. 5

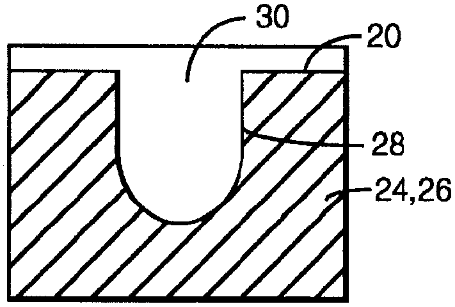

FIG. 6A

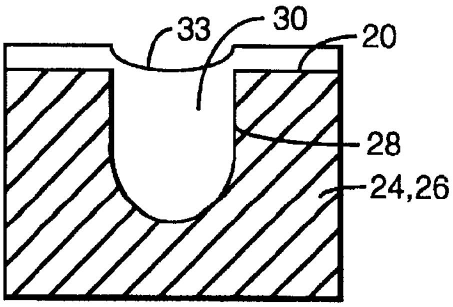

FIG. 6B

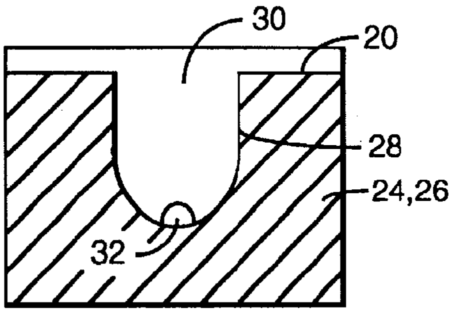

FIG. 6C

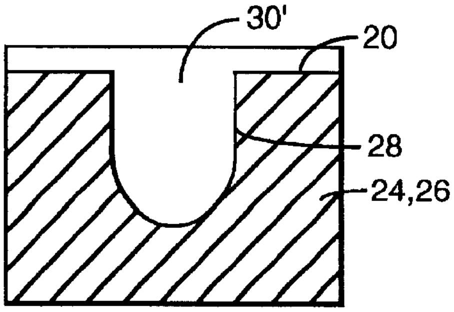

FIG. 7A

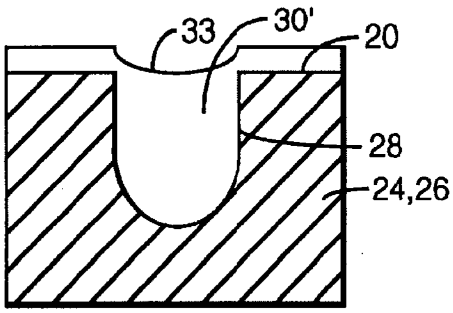

FIG. 7B

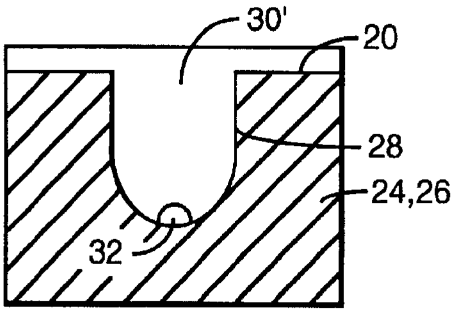

FIG. 7C

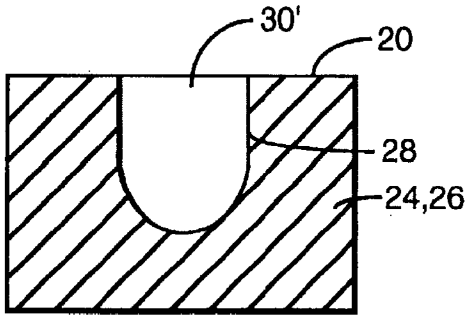

FIG. 8A

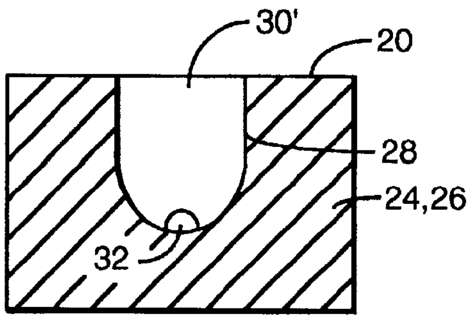

FIG. 8B

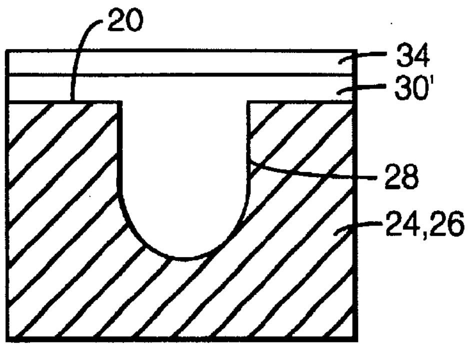

FIG. 9A

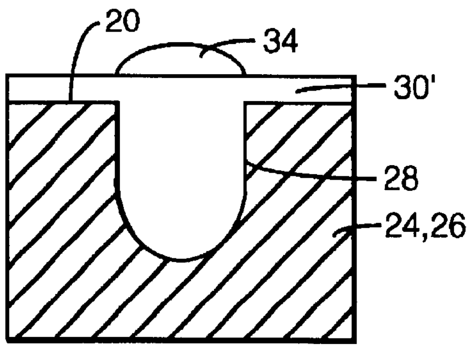

FIG. 9B

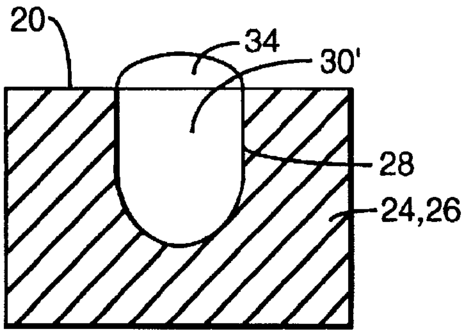

FIG. 9C

METHODS OF COATING AN IMPLANTABLE DEVICE HAVING DEPOTS FORMED IN A SURFACE THEREOF

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to implantable devices, examples of which include stents and grafts. More particularly, the present invention is directed to a method of coating an implantable device having a plurality of depots formed in a surface thereof.

2. Description of the Related Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress the atherosclerotic plaque of the lesion against the inner wall of the artery to dilate the lumen. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the vessel after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, an implantable device, examples of which include stents and grafts, may be implanted.

Stents are scaffoldings, usually cylindrical or tubular in shape, which function to physically hold open and, if desired, to expand the wall of the vessel. Typically stents are capable of being compressed, so that they may be inserted through small cavities via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in patent literature disclosing stents include U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco, and U.S. Pat. No. 4,886,062 issued to Wiktor.

Synthetic vascular grafts are vessel-like configurations that may be positioned into the host blood vessel as a replacement for a diseased or occluded segment that has been removed. Alternatively, a graft may be sutured to the host vessel at each end so as to form a bypass conduit around a diseased or occluded segment of the host vessel.

Although stents and grafts are significant innovations in the treatment of occluded vessels, there remains a need for administering therapeutic substances to the treatment site. Systemic administration of the therapeutic substance often produces adverse or toxic side effects for the patient. Local delivery of therapeutic substances, by contrast, provides a smaller overall dosage that is concentrated at a specific site. Local delivery can produce fewer side effects and achieve more effective results in many cases.

One technique for the local delivery of therapeutic substances employs medicated coatings on implantable devices. A typical method for medicating an implantable device includes applying a composition containing a polymer, a solvent, and a therapeutic substance to the implantable device using conventional techniques, such as spray-coating or dip-coating. The method further includes removing the solvent, leaving on the implantable device surface a coating of the polymer with the therapeutic substance impregnated in the polymer.

A recently developed type of stent includes a plurality of pores, called "depots" herein, that are formed in the outer surface of the stent. When such stents are coated using conventional methods, undesirable pockets of air can become trapped in the depots. Accordingly, a new coating method is needed for implantable devices having such depots.

SUMMARY OF THE INVENTION

The present invention provides methods by which implantable devices, such as stents and grafts, having a plurality of depots formed in a first surface thereof may be coated with therapeutic substances, among other possibilities.

An exemplary method within the present invention includes applying a composition including a polymer and a solvent to the first surface of the implantable device proximate to the depots. The application of the composition is performed at a first gas pressure. The method further includes applying a second gas pressure to the implantable device, wherein the second gas pressure is greater than the first gas pressure. Applying such an increased gas pressure drives the composition into the depots and eliminates, or at least reduces the size of, air pockets within the depots. The method also includes removing the solvent from the composition on the implantable device so that a stable, polymer-based coating is formed on the first surface and within the depots of the implantable device.

In some embodiments, the composition additionally includes a therapeutic substance. The therapeutic substance may be selected from antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, and antiallergic substances and combinations thereof. Alternatively, the therapeutic substance may be a radioactive isotope or a radiopaque substance.

These and other aspects of the present invention may be better appreciated in view of the detailed description and drawings of the exemplary embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a flowchart illustrating exemplary methods of coating an implantable device having depots formed in a surface thereof.

FIG. 2A is a perspective view of an implantable device with a central hollow bore.

FIG. 2B is a cross-sectional side view of the implantable device of FIG. 2A taken along line 2B—2B of FIG. 2A.

FIG. 2C is a side view of the implantable device of FIG. 2B taken along line 2C—2C of FIG. 2B.

FIG. 3A is a side view of an exemplary stent formed of thread elements engaged to one another by connecting elements.

FIG. 3B is an enlarged view of section 3B of the stent of FIG. 3A, wherein the thread elements and connecting elements have depots formed therein.

FIG. 3C is a cross-sectional view of a depot within the stent of FIG. 3B taken along line 3C—3C of FIG. 3B.

FIGS. 4A, 4B, 4C, and 4D illustrate the stent of FIG. 3C after the composition has been applied.

FIG. 5 illustrates the application of an increased gas pressure to the implantable device of FIG. 2A following application of the composition.

FIGS. 6A, 6B, and 6C illustrate the composition-coated stent of FIG. 4A after an increased gas pressure has been applied such that the composition is driven into the depot.

FIGS. 7A, 7B, and 7C illustrate the stents of FIGS. 6A, 6B, and 6C, respectively, after the solvent has been removed from the composition to form a coating.

FIG. 8A illustrates the stent of FIG. 6A after surplus composition or coating has been removed from areas other than within the depot.

FIG. 8B illustrates the stent of FIG. 6C after surplus composition or coating has been removed from areas other than within the depot.

FIG. 9A illustrates the stent of FIG. 7A after a topcoat has been applied over the coated depot and along the coated outer surface.

FIG. 9B illustrates the stent of FIG. 7A after a topcoat has been applied over the coated depot.

FIG. 9C illustrates the stent of FIG. 8A after a topcoat has been applied over the coated depot.

DETAILED DESCRIPTION

The present invention provides methods of applying a coating to an implantable device, i.e., a device that is designed to be implanted in a human or animal body, where the implantable device has depots formed in the outer surface thereof. The coating so applied may be polymer-based and may include any therapeutic substance. The present invention provides both effective and economical means for preparing implantable devices that have the capability of delivering therapeutic substances.

FIG. 1 illustrates a method **100** of coating an implantable device having depots formed in a surface thereof. In act **101** of method **100**, a composition including a polymer and a solvent is applied to a first surface of the implantable device. Act **101** is performed at a first gas pressure. The composition may further include a therapeutic substance. In act **102**, a second gas pressure is applied to the composition-coated implantable device, wherein the second gas pressure is greater than the first gas pressure at which act **101** is performed. The increased gas pressure forces pockets of air out of the depots. The solvent is removed from the composition on the implantable device in act **103** to form a coating. The composition or the coating may be removed from portions of the implantable device outside of the depots in acts **104** and **105**, respectively, thereby yielding an implantable device having a coating solely within the depots. In addition, a polymeric topcoat containing a solvent may be applied on at least a portion of the coating in act **106**. The solvent is removed from the topcoat in act **107**.

Implantable Device

The implantable device used in conjunction with the present invention may be any implantable device, examples of which include self-expandable stents, balloon-expandable stents, and grafts, among other possibilities. The implantable device can be made of a metallic material or an alloy such as, but not limited to, stainless steel, "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. The implantable device may also be made from bioabsorbable or biostable polymers. A polymeric implantable device should be chemically compatible with any substance to be loaded onto the implantable device.

FIGS. 2A, 2B, and 2C provide views of an exemplary implantable device **10**, e.g., a stent or graft. Implantable device **10** is a generally tubular structure that includes a body **12** having a first end **14** and an opposing second end **16**. A central hollow bore **18** extends longitudinally through body **12** from first end **14** to second end **16**, giving body **12** a thickness t_1 between an outer surface **20** and an inner surface **22**. Implantable device **10** can have any suitable length l_1. The values of length l_1 and thickness t_1, depend, for example, on the procedure for which implantable device **10** is used.

The surface properties of implantable device **10** may vary according to the desired use of implantable device **10**. In some embodiments, inner surface **22** and/or outer surface **20** of implantable device **10** is polished using conventional electropolishing methods, abrasive slurry methods, or other polishing methods known to those of ordinary skill in the art. In other embodiments, portions of outer surface **20** are roughened by the creation of asperities while inner surface **22** remains smooth. Asperities can be created by projecting a stream of pressurized grit onto outer surface **20**. Asperities can also be formed by removing material from outer surface **20**, for example, by chemical etching with or without a patterned mask. Alternatively, asperities can be formed by adding material to outer surface **20**, for example, by welding powder to outer surface **20** or by sputtering onto outer surface **20**.

FIG. 3A is a side view of a stent, which is an exemplary type of implantable device **10**. In FIG. 3A, body **12** is formed from a plurality of struts **24** each having arms **25** and a link **26**. Arms **25** of neighboring struts **24** are engaged to one another by links **26**. However, the underlying structure of implantable device **10** can be of virtually any design.

FIG. 3B illustrates the portion of the exemplary implantable device **10** shown in circle 3B of FIG. 3A. FIG. 3B shows that arms **25** and link **26** of strut **24** have a plurality of depots **28** formed in outer surface **20**. Depots **28**, which may also be referred to as pores or cavities, can be formed in virtually any implantable device **10** structure at any preselected location within implantable device **10**. The location of depots **28** within implantable device **10** varies according to intended usage and application. Depots **28** may be formed on implantable device **10** by exposing outer surface **20** to an energy discharge from a laser, such as, but not limited to, an excimer laser. Alternative methods of forming such depots **28** include, but are not limited to, physical and chemical etching techniques. Such techniques are well-known to one of ordinary skill in the art.

FIG. 3C is a cross-sectional view of a single depot **28** of FIG. 3B. Depot **28** may have any preselected depth d, width w, and geometrical configuration. Depth d and width w of depot **28** typically depend on the material and dimensions of implantable device **10** and the type and amount of substances deposited within depot **28** as well as on the clinical purpose and usage of implantable device **10**. Depth d and width w of the individual depots **28** formed on a single implantable device **10** can vary relative to one another.

Depot **28** may be formed in a variety of selected geometrical shapes including, but not limited to, generally cylindrical shapes, generally conical shapes, generally round shapes, elongated trenches, and irregular shapes.

Composition

A composition to be applied to implantable device **10** is prepared by conventional methods wherein all components are combined and blended. More particularly, in accordance with one embodiment, a predetermined amount of a polymer is added to a predetermined amount of a solvent. The term polymer is intended to include a product of a polymerization reaction inclusive of homopolymers, copolymers, terpolymers, etc., whether natural or synthetic, including random, alternating, block, graft, crosslinked, hydrogels, blends, compositions of blends and variations thereof.

The polymer should be biocompatible, for example a polymeric material which, in the amounts employed, is non-toxic and chemically inert as well as substantially non-immunogenic and non-inflammatory. Suitable polymeric materials include, but are not limited to, bioabsorbable polymers, biomolecules, and biostable polymers. A bioabsorbable polymer breaks down in the body and is not present sufficiently long after delivery to cause an adverse local response. Bioabsorbable polymers are gradually absorbed or eliminated by the body by hydrolysis, metabolic process, bulk, or surface erosion. Examples of bioabsorbable materials include, but are not limited to, polycaprolactone (PCL), poly-D, L-lactic acid (DL-PLA), poly-LM-lactic acid (L-PLA), poly(lactide-co-glycolide), poly (hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polyorthoester, polyanhydride, poly(glycolic acid), poly (glycolic acid-cotrimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly (amino acids), cyanoacrylates, poly(trimethylene carbonate), poly (iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, polyiminocarbonates, and aliphatic polycarbonates. Biomolecules such as heparin, fibrin, fibrinogen, cellulose, starch, and collagen are typically also suitable. A biostable polymer does not break down in the body, and thus a biostable polymer is present in the body for a substantial amount of time after delivery unless some modification is made to allow the polymer to break down. Examples of biostable polymers include, but are not limited to, PARYLENE, PARYLAST, polyurethane (for example, segmented polyurethanes such as BIOSPAN), polyethylene, polyethlyene teraphthalate, ethylene vinyl acetate, silicone, and polyethylene oxide.

The solvent can be any single solvent or a combination of solvents capable of dissolving the polymer. The particular solvent or combination of solvents selected is dependent on factors such as the material from which implantable device **10** is made and the particular polymer selected. Representative examples of suitable solvents include, but are not limited to, aliphatic hydrocarbons, aromatic hydrocarbons, alcohols, ketones, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), dihydrofuran (DHF), dimethylacetamide (DMAC), acetates and combinations thereof.

The addition of the polymer to the solvent may be conducted at ambient pressure and under anhydrous atmosphere. If necessary, gentle heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent, for example about 12 hours in a water bath at about 60° C.

The polymer can constitute from about 0.5% to about 20%, or more particularly from about 5% to about 10%, by weight of the total weight of the composition, and the solvent can constitute from about 80% to about 99.5%, or more particularly from about 90% to about 95%, by weight of the total weight of the composition. A specific weight ratio is dependent on factors such as the material from which implantable device **10** is made, the geometrical structure of implantable device **10** and of depots **28**, the particular polymer or combination of polymers selected, the particular solvent or combination of solvents selected, the solubility of the selected polymer(s) in the selected solvent(s), and the method by which the composition will be applied to implantable device **10**.

In accordance with another embodiment, sufficient amounts of a therapeutic substance or a combination of therapeutic substances are dispersed in the blended composition of the polymer and the solvent. In this embodiment, the polymer can constitute from about 0.5% to about 20% by weight of the total weight of the composition, the solvent can constitute from about 60% to about 99.4% by weight of the total weight of the composition, and the therapeutic substance can constitute from about 0.1% to about 20% by weight of the total weight of the composition. More particularly, the concentration of the therapeutic substance in the composition may be from about 1–9 times the concentration of the polymer in the composition.

In addition to the factors listed above, selection of a specific weight ratio of the polymer and the solvent in embodiments in which a therapeutic substance is employed is dependent on factors such as the type and amount of therapeutic substance employed. The particular weight percentage of a therapeutic substance mixed within the composition depends on factors such as the type of therapeutic substance selected, the solubility of the selected therapeutic substance, the duration of the release, the cumulative amount of release, and the release rate that is desired.

The therapeutic substance may be in true solution or saturated in the composition. If the therapeutic substance is not completely soluble in the composition, operations such as gentle heating, mixing, stirring, and/or agitation can be employed to effect homogeneity of the residues. However, care should be taken to ensure that the use of heat to effect dissolution does not also cause denaturation of a heat-sensitive therapeutic substance such as, but not limited to, a proteinaceous therapeutic substance.

Alternatively, the therapeutic substance may be encapsulated in a sustained delivery vehicle such as, but not limited to, a liposome or an absorbable polymeric particle. The preparation and use of such sustained delivery vehicles are well known to those of ordinary skill in the art. The sustained delivery vehicle containing the therapeutic substance is then suspended in the composition.

Inclusion of the therapeutic substance in the composition should not adversely alter the therapeutic substance's composition or characteristic. Accordingly, the particular therapeutic substance is selected for mutual compatibility with the other components of the composition.

In some embodiments, the therapeutic substance includes, but is not limited to, antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, antiallergic, antiangiogenic, and angiogenic substances as well as combinations thereof. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g., TAXOL by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g., TAXOTERE from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g., ADRIAMYCIN from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g., MUTAMYCIN from Bristol-Myers Squibb Co., Stamford, Conn.) Examples of such suitable antiinflammatories include glucocorticoids such as dexamethasone, methylprednisolone, hydrocortisone and betamethasone, superpotent glucocorticoids such as clobustasol, halobetasol, and diflucortolone, and non-steroidal antiinflammatories such as aspirin, indomethacin and ibuprofen. Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as ANGIOMAX (Biogen, Inc., Cambridge, Mass.) Examples of such cytostatic or antiproliferative agents include actinomycin D as well as derivatives and analogs thereof (manufactured by Sigma-Aldrich, Milwaukee, Wis.; or COSMEGEN available from Merck & Co., Inc., Whitehouse Station, N.J.), angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g., CAPOTEN and CAPOZIDE from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g., PRINIVIL and PRINZIDE from Merck & Co., Inc., Whitehouse Station, N.J.); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name MEVACOR from Merck & Co., Inc., Whitehouse Station, N.J.), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example-of an antiallergic agent is permirolast potassium. Examples of antiangiogenic agents include thalidomide and angiostatin. Examples of angiogenic agents include vascular endothelial cell growth factor (VEGF) and fibroblast growth factor (FGF). Examples of arteriogenic agents include histimine, MCP-1, lipo-polysaccharide, and β-FGF. Other therapeutic substances or agents that may be used include alpha-interferon, genetically engineered epithelial cells, and dexamethasone. While the preventative and treatment properties of the foregoing therapeutic substances or agents are well-known to those having ordinary skill in the art, the substances or agents are provided by way of example and are not meant to be limiting. Other therapeutic substances are equally applicable for use with the disclosed methods and compositions.

In other embodiments, the therapeutic substance may be a radioactive isotope. Examples of radioactive isotopes include, but are not limited to, phosphorus (p^{32}), palladium (Pd^{103}), cesium (Cs^{131}), and iodine (I^{125}).

In still other embodiments, the therapeutic substance is a nucleic acid or a protein. Examples of such nucleic acids include phosphorodiamidate morpholino oligomers (PMO), cyclic-3'-5'-adenosine monophosphate (8-C1-cAMP), Antisense oligonucleotides, and various nucleic acids encoding for growth factors such as vascular endothelial cell growth factor (VEGF) and fibroblast growth factor (FGF). Examples of proteins include growth factors such as VEGF and FGF.

In addition, the composition may include more than one therapeutic substance. In such embodiments, the number, type, and ratio of therapeutic substances within the composition are treatment-specific. However, the substances within the composition should be mutually compatible, such that the characteristics, effectiveness, and physical structure of the substances are not adversely altered. Therapeutic substances that are not mutually compatible should be isolated from one another within the composition by, for example, encapsulating one or both of the therapeutic substances within separate sustained delivery vehicles.

In still other embodiments, the composition may include a radiopaque substance. Such substances help to facilitate implantable device usage in radiotherapeutic procedures. A example of a radiopaque substance is gold.

As described further below, the composition is applied to implantable device **10** to form a coating thereon.

Coating the Implantable Device

a. Application of the Composition

Prior to applying the composition to implantable device **10**, outer surface **20** and depots **28** should be clean and free from contaminants that may be introduced during manufacturing. However, outer surface **20** and depots **28** of implantable device **10** require no particular pretreatment to retain the applied coating.

Referring again to FIG. **1**, the above-described composition is applied to implantable device **10** at a first gas pressure in act **101** of method **100**. Typically, the gas pressure at which the composition is applied to implantable device **10** is ambient pressure. However, any gas pressure at which the composition may be properly applied to implantable device **10** is suitable for use with the embodiments of the present invention. The composition may be applied to implantable device **10** by any conventional method, such as by spraying the composition onto implantable device **10** or immersing implantable device **10** in the composition. Variations of spray and immersion techniques are also suitable methods of applying the composition to implantable device **10**. In one such variation, the composition may be applied by first spraying or immersing implantable device **10** as described above. The composition-coated implantable device **10** is then centrifuged. The rotation of implantable device **10** creates a centrifugal force upon the composition applied to implantable device **10**. This centrifugal force causes excess accumulations of the composition to be more evenly redistributed over implantable device **10** and thus provides a more even, uniform coating of the composition on implantable device **10**. The rotational speed during centrifugation can be varied. Higher RPM values may provide improved uniformity and a reduction in defects. However, lower RPM values improve the total loading of the composition onto implantable device **10**. Increasing the total centrifuigation time may also improve the uniformity and reduce defects in the coating of the composition on implantable device **10**.

As mentioned above, and as shown in FIGS. **4A–4D**, undesirable air pockets **32** form in depots **28** when conventional coating methods are used. The air pockets **32** prevent composition **30** from completely filling depots **28**. For example, FIG. **4A** depicts an embodiment in which composition **30** is deposited solely on outer surface **20**. Depot **28** contains an air pocket **32** rather than composition **30**. Alternatively, some amount of composition **30** may enter depot **28** such that depot **28** is from about 0.1% to about 50% filled with composition **30**. The portion of depot **28** not filled with composition **30** typically contains an air pocket **32**. Air pocket **32** within depot **28** may form above, between, or below areas containing composition **30**, as depicted in FIGS. 4B, 4C, and 4D, respectively. The amount of composition **30** that enters depot **28**, if any, depends, in part, on the geometry of depot **28** and the surface tension of composition **30**.

b. Application of an Increased Gas Pressure

As depicted in FIGS. **1** and **5**, an increased gas pressure P is uniformly applied to the composition 30-coated implantable device **10** in act **102**. Gas pressure P is any gas pressure greater than the gas pressure at which act **101** is performed as described above. Gas pressure P may be greater than atmospheric pressure. By way of example and not limitation, gas pressure P ranging from about 29.4 PSI (203 kPa) to about 58.8 PSI (405 kPa) may be applied to implantable device **10** from all directions for a duration ranging from about 0.5 minute to about 20 minutes.

The actual gas pressure P selected depends, at least in part, on the viscosity of composition **30**. Compositions **30** having higher viscosities, e.g., 20% polymer by weight, typically require using higher gas pressures, e.g., 58.8 PSI (405 kPa), while compositions **30** having lower viscosities, e.g., 0.5% polymer by weight, typically require using lower gas pressures, e.g., 29.4 PSI (203 kPa). Regardless of the viscosity of composition **30**, the gas pressure P applied should not be so high as to cause phase separation or precipitation.

The duration for which gas pressure P is applied depends, in part, on the viscosity of composition **30** and the actual gas pressure P applied. Compositions **30** having higher viscosities, e.g., 20% polymer by weight, typically require that gas pressure P be applied for a longer duration, e.g., 10 minutes, while compositions **30** having lower viscosities, e.g., 0.5% polymer by weight, typically require that gas pressure P be applied for a shorter duration, e.g., 0.5 minute. Similarly, higher gas pressures, e.g., 58.8 PSI (405 kPa), typically are applied for a shorter duration, e.g., 5 minutes, while lower gas pressures, e.g., 29.4 PSI, typically are applied for a longer duration, e.g., 20 minutes.

The gas utilized in the application of gas pressure P may be air, carbon dioxide, nitrogen, or any other gas suitable for use with implantable device **10** and composition **30**. The source of gas pressure P may be any suitable source capable of applying the appropriate amount of gas pressure P for the appropriate duration to implantable device **10** uniformly from all directions as discussed above. One example of a suitable source of gas pressure P is a sealable pressure chamber into which the composition 30-coated implantable device **10** may be placed in entirety.

Gas pressure P drives composition **30** into depots **28** of implantable device **10**. As a result, composition **30** may completely displace air pocket **32** within depot **28** such that depot **28** becomes completely filled with composition **30**, as depicted in FIGS. **6**A and **6**B. In other embodiments, composition **30** may partially displace air pocket **32**, or alternatively compress air pocket **32** such that air pocket **32** occupies a smaller portion of depot **28** after the pressure treatment than before the pressure treatment, as depicted in FIG. **6**C.

Composition **30** may not be of uniform thickness along outer surface **20** following the pressure treatment in act **102**. For example, as shown in FIG. **6**B, a dimple **33** may form in composition **30** above depot **28**.

c. Removal of the Solvent from the Composition

The solvent is removed from composition **30** on implantable device **10** in act **103**. The solvent may be removed using techniques such as, but not limited to, evaporation at ambient pressure and room temperature in an anhydrous atmosphere for 48 hours, or exposure to mild heat, e.g., 60–65° C., under vacuum conditions. In embodiments where implantable device **10** is made of a bioabsorbable polymer, the solvent should be removed relatively quickly to avoid prolonged exposure and thereby ensure the mechanical integrity of the implantable device **10**. Upon removal of essentially all of the solvent, a stable polymeric coating **30'** remains on implantable device **10**, including on outer surface **20** and within depots **28**, as depicted in FIGS. 7A, 7B, and 7C.

In some embodiments, application of increased gas pressure P in act **102** continues during the removal of solvent from composition **30** in act **103**. In such embodiments, components of composition **30** other than the solvent, i.e., polymeric material and any therapeutic substances, will adhere to the interior surface of depot **28**. Thus, when the gas pressure upon implantable device **10** is reduced following the removal of solvent from composition **30**, any air pocket **32** remaining trapped within depot **28** will not expand, but rather, will retain its reduced size.

d. Optional Removal of the Composition or the Coating from Outer Surface

It may be desirable to treat implantable device **10** so that coating **30'** is present only within depots **28**, and not on outer surface **20** around depots **28**, as depicted in FIGS. **8**A and **8**B. To obtain such embodiments, undesirable portions of composition **30** may be removed prior to the removal of the solvent. Alternatively, undesired portions of coating **30'** may be removed after coating **30'** is formed by removal of the solvent.

Conventional techniques, such as, but not limited to, scraping, squeegeeing, washing, blowing, or spinning may be used to remove the undesired portions of composition **30** or coating **30'**. The scraping method involves the mechanical stripping of composition **30** or coating **30'** from outer surface **20** using, for example, a brush. The squeegeeing method involves passing implantable device **10** through an opening in a sponge filled with cleaning solution containing liquids such as, but not limited to, water, ethanol, DMSO, or hexane. The washing method may involve soaking implantable device **10** in a cleaning solution containing liquids such as, but not limited to, water, ethanol, DMSO, or hexane. Alternatively, the washing method may involve rinsing implantable device **10** having coating **30'** thereon with the same solvent used in composition **30**. The washing methods may or may not include sonication. The blowing method may include passing air pressure over outer surface **20** having composition **30** thereon such that compostion **30** or coating **30'** is blown offouter surface **20**. The spinning methods may include spinning implantable device **10**, such as by centrifugation, so as to drive composition **30** off outer surface **20**. Of course, care should be taken during the removal of composition **30** or coating **30'** from outer surface **20** such that composition **30** or coating **30'** is not also removed from within depot **28**.

e. Optional Use of Topcoats

In some embodiments, a polymeric topcoat **34**, with or without a therapeutic substance therein, is deposited over coating **30'** on implantable device **10** in act **106**, as depicted in FIGS. 9A, 9B, and 9C. FIG. 9A illustrates an embodiment in which topcoat **34** is applied over coated outer surface **20** as well as above coated depot **28**. In alternative embodiments depicted in FIGS. 9B and 9C, topcoat **34** is applied solely above coated depot **28**. Polymeric topcoat **34** can be applied in act **106** by any conventional method, such as the immersion or spray techniques described above with reference to the application of composition **30**.

Polymeric topcoat **34** will typically reduce the rate of release of a substance or substances from implantable device **10**. The polymers that were listed above with reference to polymers suitable for inclusion in composition **30** are equally applicable here. By way of example, and not limitation, the polymeric topcoat **34** can have a thickness of about 0.25 microns to about 1.5 microns. Typically, topcoat **34** can have a thickness of about 1 micron. It will be appreciated by one of ordinary skill in the art that the thickness of the polymeric topcoat **42** is based on factors such as the type of procedure for which implantable device **10** is employed and the rate of release that is desired.

In act **107** of method **100**, any solvent within topcoat **34** is removed following application to implantable device **10**. Removal of the solvent from topcoat **34** may be accomplished using conventional methods known to one of ordinary skill in the art, such as those listed above with reference to the removal of solvent from composition **30**, which are equally applicable here.

Methods of Use

As mentioned above, implantable devices that may be treated according to the methods of the present invention include stents and grafts, among other possibilities. An implanted stent or graft having the above-described coating is useful for treating occluded regions of blood vessels caused by thrombosis and/or restenosis, among other possible uses.

Stents may be placed in a wide array of blood vessels, both arteries and veins. Briefly, an angiography is first performed to determine the appropriate positioning for stent therapy. Angiography is typically accomplished by using a catheter to inject a radiopaque contrasting agent into an artery or vein as an X-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above described covering may then be expanded at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

Vascular grafts may be used to replace, bypass, or reinforce diseased or damaged sections of a vein or artery. The general procedure for implantation includes the step of pre-clotting, wherein the graft is immersed in the blood of the patient and allowed to stand for a period of time sufficient for clotting to ensue. After pre-clotting, hemorrhaging is less likely to occur when the graft is implanted, and thus the growth of tissue is not impeded. Grafts may be placed either through invasive surgery or non-invasively through percutaneous endoluminal transport. Percutaneous delivery of a graft avoids the complications and risks of surgery. The graft may be attached to the vessel at each end of the diseased region, thus bypassing the diseased region. Alternatively, the diseased region may be removed and replaced by the graft.

While particular embodiments and applications of the present invention have been shown and described, those of ordinary skill in the art will appreciate that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

We claim:

1. A method of depositing a polymer into a plurality of depots formed in an outer surface of a stent comprising:

applying a composition comprising a polymer and a solvent to said plurality of depots, wherein said act of applying said composition is performed at a first gas pressure;

applying a second gas pressure to said composition in said depots, wherein said second gas pressure is greater than said first gas pressure and less than the pressure which causes phase separation or precipitation of said polymer in said composition, and wherein said second gas pressure is sufficient to remove air pockets from said composition in said depots; and

removing said solvent from said composition, wherein a polymeric deposit is formed substantially free from air pockets in said depots of said stent.

2. The method of claim **1**, wherein said composition comprises a therapeutic substance.

3. The method of claim **2**, wherein said therapeutic substance is selected from a group consisting of antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, and antiallergic substances and combinations thereof.

4. The method of claim **2**, wherein said therapeutic substance is selected from a group consisting of radioisotopes and radiopaque substances.

5. The method of claim **1**, wherein said second gas pressure is a gauge pressure of about 29.4 PSI to about 58.8 PSI.

6. The method of claim **1**, wherein said second gas pressure is greater than atmospheric pressure.

7. The method of claim **1**, wherein the act of applying said composition to said depots comprises applying said composition to said stent and allowing said composition to penetrate into said depots.

8. The method of claim **7**, further comprising removing said composition from portions of said outer surface of said stent outside of said depots.

9. The method of claim **1**, further comprising applying a polymeric topcoat at least over said depots.

10. The method of claim 1, wherein said second pressure is applied for a duration of about 0.5 minutes to about 20 minutes.

11. The method of claim **1**, wherein said first pressure is at least atmospheric pressure.

12. A method of loading a substance into a plurality of depots of a stent comprising:

applying a composition including a polymer and a solvent to said depots, said composition having a polymer content between about 0.5% and 20% by weight, and wherein said act of applying said composition is performed at a first gas pressure of at least atmospheric pressure;

placing the stent in a sealable pressure chamber; and

applying a second gas pressure to said composition, said second gas pressure being a gauge pressure of about 29.4 PSI to about 58.8 PSI, wherein said second gas pressure is greater than said first gas pressure and less than the pressure which causes phase separation or precipitation of said polymer in said composition and is sufficient to remove air pockets from said composition in said depots.

13. The method of claim **12**, wherein said polymer is selected from a group consisting of bioabsorbable polymers, biomolecules, and biostable polymers.

14. The method of claim **13**, wherein said composition further comprises a therapeutic substance.

15. The method of claim 14, wherein said therapeutic substance is selected from a group consisting of antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, and antiallergic substances and combinations thereof.

16. The method of claim 14, wherein said therapeutic substance is selected from a group consisting of radioisotopes.

17. The method of claim 14, further comprising applying a polymeric topcoat over said depots.

18. The method of claim 12, further comprising removing said solvent from said composition.

19. The method of claim 12, wherein said second pressure is applied for a duration of about 0.5 minutes to about 20 minutes.

20. A method of depositing a substance in depots of an implantable device, comprising:

applying said substance in a liquid carrier to said device wherein said substance and said liquid carrier are allowed to penetrate into said depots;

placing said device in a sealable pressure chamber;

applying a first pressure greater than atmospheric pressure to said device so as to significantly reduce the size of the air pockets in said depots;

removing said liquid carrier from said device while applying a second pressure greater than atmospheric pressure to maintain the reduced size of the air pockets; and

applying a third pressure to said device subsequent to said removal of said liquid carrier wherein said third pressure is less than said first and second pressures.

21. The method of claim 20, wherein said substance is a polymer.

22. The method of claim 20, wherein said substance is a drug.

23. The method of claim 20, wherein said substance is a mixture of a polymer and a drug.

24. The method of claim 20, wherein said first pressure does not cause phase separation or precipitation of said substance in said liquid carrier.

25. The method of claim 20, wherein said first pressure is equal to said second pressure.

26. The method of claim 20, wherein said application of said substance is performed while said device is in said pressure chamber.

27. A method of depositing a substance in depots of a stent, comprising:

applying a composition including a substance to said stent wherein said composition penetrates into said depots of said stent; and

applying a pressure to said composition to essentially remove air pockets or reduce the size of air pockets from said composition in said depots, wherein said pressure does not cause phase separation or precipitation of said substance in said composition in said depots of said stent.

28. The method of claim 27, wherein said substance includes a drug.

29. The method of claim 27, wherein said substance includes a polymer.

30. The method of claim 27, wherein said substance is a mixture of a polymer and a drug.

31. The method of claim 27, wherein said composition includes a solvent and wherein said method additionally comprises allowing said solvent to evaporate.

32. A method of depositing a substance in depots of an implantable device, comprising:

applying said substance in a liquid carrier to said device wherein said substance and said liquid carrier are allowed to penetrate into said depots;

placing said device in a sealable pressure chamber;

applying a first pressure to said device so as to significantly eliminate or reduce the size of the air pockets in said depots;

removing said liquid carrier from said device; and

applying a second pressure to said device subsequent to said removal of said liquid carrier wherein said second pressure is less than said first pressure.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,763	10/02/2003	Evgenia Mandrusov	50623.341	1625

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EXAMINER	
CAMERON, ERMA C	
ART UNIT	**PAPER NUMBER**
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10/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/678,763	**Applicant(s)** MANDRUSOV ET AL.	
	Examiner /Erma Cameron/	**Art Unit** 1792	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _07 August 2007_.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under _Ex parte Quayle_, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _23-77_ is/are pending in the application.

4a) Of the above claim(s) _24-29,33-44,46-55,61-63 and 67-77_ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _23, 30-32, 45, 56-60, 64-66_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Election/Restrictions

1. Applicant's election without traverse of A) the angiogenic substance of claim 45, B) iii and C) vi in the reply filed on 8/7/2007 is acknowledged.

Claims 24-29, 33-44, 46-55 and 61-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 67-77 were previously withdrawn from consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. The rejection of Claims 32, 59 and 60 under 35 U.S.C. 112, second paragraph, is withdrawn because of the amendment filed 8/7/2007.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 64 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 64 had originally claimed "covering the inner surface", and was amended 8/7/2007 to read "temporarily placing a cover on the inner surface", which implies a "touching" relationship between the cover and the inner surface. This is new matter that is not supported by the specification as originally filed.

The applicant is requested to cancel new matter.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

> subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 23, 32, 56 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Ragheb et al. (US 6,299,604).

Ragheb et al. ('604) teach a method of manufacturing a drug-eluting coating for a stent (col.6, line 65), the stent including a lumen (col. 7, line 1-2), i.e. tubular body having an outer surface and an inner surface (col.8, line 1-5). Ragheb et al. ('604) disclose that at least one bioactive material, i.e. the first coating, is posited (col. 7, line 65-67) on one surface of the structure and other surface will contain different bioactive materials, i.e. second coating. In this manner (col. 8, line 1-5) one or more bioactive materials or drugs may be delivered with a vascular stent to the blood stream from the lumen surface, i.e. inner surface of the stent, and a different treatment may be delivered on the vessel surface, i.e. outer surface of the stent. Ragheb et al. ('604) further teach (col. 4, line 61-64) the same bioactive material will generally not be posited on the different surfaces of the stent. In the other words, each surface of the stent structure will carry a different bioactive material.

Additionally, Ragheb et al. ('604) teach a range of drugs, medicaments and materials may be employed as the coating materials (col. 8, line 7-8), such as (col. 9, line 34-36) angioenine, i.e. an angiogenic substance and (col. 14, line 47-48), antiproliferative agent such as pacitaxel, which is capable of inhibiting smooth muscle cells proliferation or migration.

Response to Arguments

The applicant has argued that Ragheb et al. do not disclose an angiogenic substance on the inner surface and an antiproliferative on the outer surface.

The examiner's position is that one of skill in the art would know to place the angiogenic substance on the inner surface (where the blood is) and the antiproliferative on the outer surface (where the blood vessel cells are).

8. Claims 23, 45, 56, 58, 59 are rejected under 35 U.S.C. 102(e) as being anticipated by Weber (US 6,517,888).

Weber ('888) teaches a method of manufacturing a drug-eluting coating for a stent (col. 5, line 21), the stent including a cylindrical body, i.e. a tubular body having an outer surface and an inner surface (col.2, line 1-2). The inner and outer surface of the stent can be coated with different materials (col. 2, line 37-38). The method comprises: forming a first coating on the inner surface of the stent (col.2, line2-3), the first composition including a first therapeutic substance capable of angiogenesis (col. 7, line 17); and applying a second composition to the outer surface of the stent, the second therapeutic substance capable of inhibiting migration or proliferation of smooth muscle cells (col.6, line 41).

As for claim 45, Weber ('888) teaches the angiogenic substance can be a hepatocyte growth factor (col. 6, line 17),

As for claim 58, Weber ('888) teaches the first and second coating materials may include a polymer (col. 5, line 35-36).

Response to Arguments

The applicant has argued that each class of agents can be placed on the outer surface or inner surface.

The examiner's position is that one of skill in the art would know to place the angiogenic substance on the inner surface (where the blood is) and the antiproliferative on the outer surface (where the blood vessel cells are).

9. Claims 23, 30-31, 64-66 are rejected under 35 U.S.C. 102(b) as anticipated by Loeffler (US 5,897,911).

Loeffler ('911) teaches a method of manufacturing a coating for a stent (col.1, line 50), the stent including a tubular body having an outer surface and an inner surface (see fig. 3) the method comprising: using a mandrel and/or mold, i.e. removable sheath to apply coating materials to the selected surfaces of the stent (col. 1, line 52-62). Loeffler ('911) teaches the coating materials including polymers (col. 2, line 54) and various therapeutic agents, antithrombins (col.3, line 6) and angiogenic substance such as fibroblast growth factor (col.3, line 21).

As for claims 64-66:

In one embodiment, Loeffler ('911) teaches the stent is first mounted about a core pin and pin cap (col.4, line 23-24, see fig. 2), after which the entire assembly is fitted inside an external mold. The coating material is subsequently injected (col.4, line 29-31) through the core pin or through the external mold to coat the inner or outer surface of the stent. Additionally, Leoffler ('911) teaches (col. 2. line 1-3) different coating materials, i.e. different therapeutic agents and different polymers, can be applied to selected surfaces of the stent..

Response to Arguments

The applicant has argued that each class of agents can be placed on the outer surface or inner surface.

The examiner's position is that one of skill in the art would know to place the angiogenic substance on the inner surface (where the blood is) and the antiproliferative on the outer surface (where the blood vessel cells are).

The applicant has additionally argued that the core pin is spaced apart from, not on, the interior surface of the stent. The examiner disagrees. Figure 3 shows a tapered mandrel 26 that fits snugly inside the stent 12.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 57 is rejected under 35 U.S.C. 103(a) as being anticipated by Ragheb et al. ('604) in view of Harish et al. (US 6,506,437).

Ragheb et al. ('604) teach that which is disclosed in the above. Ragheb et al. teach coating a drug-eluting stent by applying angiogenic substance on the inner surface of the stent and an antiproliferative agent on the outer surface of the stent. Ragheb et al. ('604) are silent concerning the stent having cavities in the inner and outer surfaces.

Harish et al. ('437) teach a method of coating implantable stent (col. 2, line 54), the stent including a tubular body having an outer surface and an inner surface (see fig.2). Additionally, the stent has a plurality of cavities formed in virtually any preselected location of the stent surface (col. 4, line 47-51), i.e. the stent has cavities in the inner and outer surfaces. Harish et al. ('437) teach applying a first coating to the outer surface of the stent (col. 2, line 23-26), wherein the coating compositions are applied to at least partially fill the cavities (col. 8, line 60-63). Harish et al. ('437) teach the coating compositions include polymers (col. 5, line 10) and therapeutic substances such as angiogenic substances, anticoagulant and antiproliferative agents (col. 6, line 60-62).

Together, Ragheb et al. ('604) teach the inner surface of the implant stent is coated with angiogenic substance that can be released to the blood stream and stimulate angiogenesis and the outer surface of the stent is coated with antiproliferative agents that are capable of exerting the therapeutic substance to the blood vessel wall to prevent the thrombosis of the artery, and Harish et al. ('437) also teach a drug-eluting implant stent that is capable of local delivery of antiproliferative agents to the blood vessel and additionally, releasing the designed therapeutic substance in the manner of controlled rate by filling drug substance in the cavities and cover with topcoat polymeric coating. Given these teaching, Harish et al. ('437) would have reasonably suggested coating the implant stent and cavities in inner and outer surfaces with the coating method of Ragheb et al. ('604).

It would have been obvious to one of ordinary skill in the art to use the stent of Harish et al. ('437) in the coating method of Ragheb et al. ('604) with the expectation of successful results because Harish et al. ('437) teach a method of delivering angiogenic and antiproliferative substance not only on the lesion site but also exerting therapeutic substances in an extended period of time.

Response to Arguments

The applicant has not presented specific arguments on this rejection.

12. The rejection of Claim 39 under 35 U.S.C. 103(a) as being unpatentable by Weber ('888) in view of Slaikeu et al. (US 6,663,607) is withdrawn because this claim has been withdrawn from consideration.

13. The rejection of Claims 42 and 52 under 35 U.S.C. 103(a) as being unpatentable by Weber ('888) in view of Bowlin et al. (US 2002/0,081,732) is withdrawn because these claims have been withdrawn from consideration.

14. The rejection of Claims 51 and 53 under 35 U.S.C. 103(a) as being unpatentable by Weber ('888) in view of Pierce et al. (US 2001/0,044,413) is withdrawn because these claims have been withdrawn from consideration.

15. The rejection of Claim 38 under 35 U.S.C. 103(a) as being unpatentable by Weber ('888) in view of Lane et al. (US 4,990,333) is withdrawn because this claim has been withdrawn from consideration.

16. The rejection of Claim 40 under 35 U.S.C. 103(a) as being unpatentable by Weber ('888) in view of Li et al. ("A peptide regulator of angiogenesis" Nat Med. 6(1), 6(3), page 49-55 (Jan and March 2000)) is withdrawn because this claim has been withdrawn from consideration.

17. The rejection of Claim 41 under 35 U.S.C. 103(a) as being unpatentable by Weber ('888) in view of Penta et al. ("Del 1 induces integrin signaling and angiogenesis by ligation of alphaVbeta3," J. Biol Chem, 16; 274 (April 1999)) is withdrawn because this claim has been withdrawn from consideration.

18. The rejection of Claims 44, 47,48 under 35 U.S.C. 103(a) as being unpatentable by Weber ('888) in view of Kovesdi et al. (US 2003/0,027,751) is withdrawn because these claims have been withdrawn from consideration.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Erma Cameron/ whose telephone number is 571-272-1416. The examiner can normally be reached on 8:30-6:00, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Timothy Meeks can be reached on 571-272-1423. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Erma Cameron/
Primary Examiner
Art Unit 1792

October 15, 2007

50623.22
Divisional Application
Docket No. 50623.341
Copy from USSN 09/846,498

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EL 701 362 141 US

STENT FOR INCREASING BLOOD FLOW TO ISCHEMIC TISSUES AND A METHOD OF USING THE SAME

Evgenia Mandrusov
Paul Consigny
Syed F.A. Hossainy
Dary Mirzaee

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to implantable medical devices, such as stents, and a method of resolving ischemia by inducing formation of new blood vessels through angiogenesis and arteriogenesis.

Description of the Background

[0002] A major component of morbidity and mortality attributable to cardiovascular disease occurs as a consequence of the partial or complete blockage of vessels carrying blood in the coronary and/or peripheral vasculature. When such vessels are occluded, various complications may result from death of tissue previously nourished by the occluded vessels or inability of the occluded vessels to transport sufficient blood supply to regions requiring high blood consumption and accompanying nutrients.

[0003] Blood vessel occlusions are commonly treated by mechanically enhancing blood flow in the affected vessels. Such mechanical enhancements are often provided by employing surgical techniques that attach natural or synthetic conduits proximal and distal to the areas of occlusion, thereby providing bypass grafts, or revascularization by various means to physically enlarge the vascular lumen at the site of occlusion. These revascularization procedures involve such devices as balloons, endovascular knives (atherectomy), and endovascular drills. The surgical approach is accompanied by significant morbidity and even mortality, while the angioplasty-type processes are complicated by recurrent stenoses in many cases.

[0004] In some individuals, blood vessel occlusion is partially compensated by the natural process of therapeutic angiogenesis, in which new vessels are formed to replace the function of the impaired vessels. These new conduits may facilitate restoration of blood flow to the deprived tissue, thereby constituting "natural bypasses" around the occluded vessels. However, some individuals are unable to generate sufficient new vessels to adequately compensate for the diminished blood flow caused by cardiovascular disease. Accordingly, it would be desirable to provide methods and systems for delivering agents to help stimulate the natural process of therapeutic angiogenesis in occluded coronary and peripheral arteries in order to treat ischemia.

SUMMARY

[0005] A stent is provided. The stent includes a tubular body having an outer surface for contacting the wall of a vessel and an inner surface. The stent also includes a first coating supported by the inner surface and containing an angiogenic substance for the release of the angiogenic substance in the vessel. In addition, the stent includes a second coating supported by the outer surface and containing a therapeutic substance for applying the therapeutic substance to the wall of the vessel.

[0006] In some embodiments, the therapeutic substance is selected from antiproliferative, antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antioxidant, and anti-migratory substances, inhibitors of matrix synthesis, and combinations thereof.

[0007] Also provided is a stent, which includes a tubular structure having an inner surface and an outer surface, for implanting in a blood vessel. The stent includes a first therapeutic substance carried by the inner surface for being released downstream with the flow of blood and a second therapeutic substance, which is different from the first therapeutic substance, carried by the outer surface for application to the blood vessel wall. The first therapeutic substance facilitates therapeutic angiogenesis, and the second therapeutic substance inhibits migration or proliferation of smooth muscle cells.

[0008] In one embodiment, the inner surface of the stent includes a plurality of cavities for releasing the first therapeutic substance when exposed to the flow of blood. In another embodiment, the inner surface includes a plurality of cavities for releasing the first therapeutic substance when exposed to the flow of blood, and the outer surface includes a plurality of cavities for applying the second therapeutic substance to the blood vessel wall.

[0009] A method for increasing blood flow to ischemic tissues located downstream from an occluded region in a blood vessel is also provided. The method includes implanting a stent in the blood vessel at a location upstream from the ischemic tissues. The stent has an inner surface carrying an angiogenic substance.

[0010] In one embodiment, the stent is positioned at a location upstream of the occluded region. In another embodiment, the stent is positioned across at least a portion of the occluded region.

[0011] In yet another embodiment, the stent additionally includes a coating disposed on the outer surface of the stent. The coating includes a therapeutic substance. In another embodiment, the stent includes cavities on the outer surface containing a therapeutic substance.

BRIEF DESCRIPTION OF THE FIGURES

[0012] Figure 1A illustrates a stent.

[0013] Figure 1B illustrates an end view of the stent of Figure 1A.

[0014] Figure 2 illustrates the stent of Figure 1B having a first coating containing an angiogenic substance formed on the inner surface.

[0015] Figure 3 illustrates the stent of Figure 2 having a second coating formed on the outer surface.

[0016] Figure 4A is the region 4A of the stent of Figure 1A illustrating a therapeutic substance in cavities formed within the outer surface.

[0017] Figure 4B illustrates the stent of Figure 4A taken along line 4B-4B in accordance with an embodiment in which the therapeutic substances are releasably contained in cavities within the inner and outer surfaces, respectively.

[0018] Figures 5A-5D illustrate a method for increasing blood flow to ischemic tissue in accordance with several embodiments of the present invention.

[0019] Figure 6 illustrates a method for increasing blood flow to ischemic tissue in accordance with another embodiment of the present invention.

DETAILED DESCRIPTION

[0020] Angiogenic substances should be understood to broadly include any proteins, peptides, and small molecules as well as cells, genes, and other substances that promote, stimulate or cause therapeutic angiogenesis. One of ordinary skill in the art is familiar with methods used to determine the angiogenic or arteriogenic activity of a substance, examples of which include the use of rabbit hind limb ischemia models and pig ameroid constrictor models. Representative examples of angiogenic substances include vascular endothelial growth factor (VEGF) in any of its multiple isoforms, fibroblast growth factors, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor beta (TGF-beta) in any of its multiple isoforms, transforming growth factor alpha (TGF-alpha), lipid factors, hypoxia-inducible factor 1-alpha (HIF-1-alpha), PR39, del 1, nicotine, insulin-like growth factors, placental growth factor (PlGF), hepatocyte growth factor (HGF), estrogen, follistatin, proliferin, prostaglandin E1, prostaglandin E2, cytokines, tumor necrosis factor (TNF-alpha), erythropoietin, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), angiogenin, hormones, and genes that encode such substances.

[0021] VEGF, a 46 kD protein, has isoforms containing 121, 165, 189, and 206 amino acids. VEGF is a heparin-binding protein that is mitogenic for endothelial cells only. This mitogen is also known as vascular permeability factor and will induce vessel leakage at doses higher than those required for angiogenic response. VEGF has been shown to induce functionally significant angiogenesis in the acute and chronic coronary ischemia models in pigs and dogs. This protein was tested in phase II clinical trials and was shown to be safe at the administered doses.

[0022] The heparin-binding fibroblast growth factor (FGF) family includes ten currently identified mitogens and four additional homologs of unknown function. FGF-2, also referred to as FGF-beta, is a 16.5 kD, 146 amino acid protein. FGF-2 is a pluripotent mitogen capable of stimulating migration and proliferation of a variety of cell types including fibroblasts, macrophages, smooth muscle cells and endothelial cells. FGF-2 can also stimulate endothelial production of various proteases including plasminogen activator and matrix metalloproteinases, induce significant vasodilation through stimulation of nitric oxide release, and promote chemotaxis. FGF-2 is present in the normal myocardium and its expression is potentiated by hypoxia or hemodynamic stress. This protein has been shown to induce functionally significant angiogenesis in the acute and chronic coronary ischemia models in pigs and dogs. FGF-2 was tested in phase II clinical trials and was shown to be safe at the administered doses. FGF-1, also referred to as FGF-alpha, is an unstable form of fibroblast growth factor that has similar action as FGF-2. However, FGF-1 is 30-100 times less potent than FGF-2.

[0023] MCP-1 is produced by shear stress-activated endothelium. Monocytes transmigrate through the vessel wall of proliferating collateral arteries and produce MCP-1, resulting in monocyte homing and acceleration of the natural process of collateral growth by degradation of the basement membrane, proliferation of smooth muscle cells and endothelial cells, and enlargement of the pre-existing vessel.

[0024] TGF-beta exists in at least five isoforms, each of which is encoded by a different gene. TGF-beta directly induces proliferation, migration and/or differentiation of endothelial cells. It has been reported that TGF-beta signaling may regulate VEGF expression in cardiac myocytes. (Zheng, et al., "Mechanisms of coronary angiogenesis in response to stretch: role of VEGF and TGF-beta," Am J. Physiol Heart Circ. Physiol, 280(2):H909-17 (February 2001).)

[0025] TGF-alpha directly induces proliferation, migration and/or differentiation of endothelial cells.

[0026] Lipid factors include spingosine 1-phosphate (S1P), which is stored in platelet granules and is released upon platelet activation, as well as lysophasphatidate (LPA) and phosphatidic acid (PA). S1P, LPA, and PA bind to endothelial differentiation gene receptors, a novel family of G-protein-coupled receptors present in endothelial cells. When stimulated, these receptors activate pathways that ultimately result in endothelial cell responses associated with angiogenesis including the liberation of endothelial cells from established monolayers, chemotactic migration, and proliferation.

[0027] HIF-1-alpha has been shown in cell culture to be a transcriptional activator for VEGF. HIF-1-alpha has been selectively expressed in areas of ischemia or infarction, but not in myocardium remote to ischemic or infarcted areas. The presence of HIF-1-alpha mRNA, and subsequently the presence of VEGF mRNA, in the heart tissue of patients with infarction is said to indicate that HIF-1-alpha contributes to limitation of infarct size by promoting angiogenesis and vascular remodeling, and that it does so by increasing steady-state levels of VEGF mRNA.

[0028] PR39, a macrophage-derived peptide, inhibits the ubiquitin-proteasome-dependent degradation of HIF-1-alpha protein, resulting in accelerated formation of vascular structures in vitro and increased myocardial vasculature in mice. Coronary flow studies in mice have demonstrated that PR39-induced angiogenesis resulted in the production of functional blood vessels. Such findings indicate that PR39 and related compounds can be used as potent inductors of angiogenesis and that selective inhibition of HIF-1-alpha degradation may underlie the mechanism of inflammation-induced angiogenesis. (Li, et al., "A peptide regulator of angiogenesis," Nat Med. 6(1), 6(3), pgs. 49-55 (January and March 2000))

[0029] Del 1, an extracellular matrix protein, encodes three Notch-like epidermal growth factor repeats: an RGD motif, and two discoidin domains. Del 1 is expressed in an endothelial cell-restricted pattern during early development. In some studies, recombinant baculovirus Del 1 protein was shown to promote alphavbeta3-dependent endothelial cell attachment and migration. Attachment of endothelial cells to Del 1 was associated with clustering of alphavbeta3, the formation of focal complexes, and recruitment of talin and vinculin into these complexes. These events were shown to be associated with phosphorylation of proteins in the focal complexes, including the time-dependent phosphorylation of p125(FAK), MAPK, and Shc. When recombinant Del 1 was evaluated in an in-ovo chick chorioallantoic membrane assay, it was found to have potent angiogenic activity. This angiogenic activity was inhibited by a monoclonal antibody directed against alphavbeta3, and an RAD mutant Del 1 protein was inactive. Thus, Del 1 has been indicated to provide a unique autocrine angiogenic pathway for the embryonic endothelium, and this function is mediated in part by productive ligation of integrin alphavbeta3. (Penta, et al., “Del l induces integrin signaling and angiogenesis by ligation of alphaVbeta3,” J. Biol Chem, 16; 274 (April 1999).)

[0030] Nicotine, via stimulation of nicotinic receptors, has been shown to enhance angiogenesis and may stimulate tumor growth in part by enhancing tumor vascularity. (Heeschen, et al., "Nicotine Stimulates Tumor Angiogenesis," Stanford University, Stanford, CA, (2001).)

[0031] Two different insulin-like growth factors have been described, IGF-1 and IGF-2. The two factors are encoded by two different genes, which are expressed differentially in different tissues and at different times of development. IGF-1 is a 150 kD peptide that is synthesized by many cell types, including smooth muscle cells. This peptide stimulates migration and tube formation by vascular endothelial cells as wells as migration and proliferation of smooth muscle cells, which are important steps in the angiogenesis process.

[0032] "Therapeutic angiogenesis" refers to the processes of causing or inducing angiogenesis and arteriogenesis.

[0033] "Angiogenesis" is defined as promotion or causation of the formation of new blood vessels.

[0034] "Arteriogenesis" is the formation of collateral vessels, which typically occurs in a non-ischemic region of a vessel. The collateral vessels allow blood to flow from a well-perfused region of the vessel into the ischemic region.

[0035] "Ischemia" is defined as localized reduction in blood flow caused by narrowing or occlusion of one or more vessels, such as coronary arteries or their branches, most often through thrombosis or via deposits of fat, connective tissue, calcification of the walls, or restenosis caused by the abnormal migration and proliferation of smooth muscle cells.

[0036] "Occlusion" is defined as the total or partial obstruction of blood flow through a vessel.

[0037] "Smooth muscle cells" include those cells derived from the medial and adventitial layers of the vessel that migrate and proliferate in intimal vascular sites.

[0038] "Migration" of smooth muscle cells means movement of these cells in vivo from the medial layers of a vessel into the intima, such as may also be studied in vitro by following the motion of a cell from one location to another, e.g., using time-lapse cinematography or a video recorder and manual counting of smooth muscle cell migration out of a defined area in the tissue culture over time.

[0039] "Proliferation" of smooth muscle cells means increase in cell number.

[0040] "Abnormal" proliferation means division, growth or migration of cells occurring more rapidly or to a significantly greater extent than typically occurs in a normally functioning cell of the same type, i.e., hyper-proliferation.

[0041] "Inhibiting" cellular activity means reducing, delaying or eliminating smooth muscle cell migration and/or proliferation that causes hyperplasia, restenosis, and vascular occlusions, particularly following biologically or mechanically mediated vascular injury or trauma or under conditions that would predispose a mammal to suffer such a vascular injury or trauma.

[0042] A stent is broadly defined to include any inter- or intra-luminal device used for the release of an active ingredient and/or for upholding the luminal patency. Examples of stents include self-expandable stents, balloon-expandable stents, and stent-grafts. The stent can be made of a metallic material or an alloy such as, but not limited to, stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. The stent can also be made from bioabsorbable or biostable polymers.

[0043] The stent can be coated with a polymeric material for the delivery of the angiogenic substance alone or in combination with a therapeutic substance. "Polymer," "poly," and "polymeric" are defined as compounds that are the product of a polymerization reaction and are inclusive of homopolymers, copolymers, terpolymers etc., including random, alternating, block, and graft variations thereof. Representative examples of polymers that can be used with the embodiments of the present invention include ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade name EVAL), poly(hydroxyvalerate); poly(L-lactic acid); polycaprolactone; poly(lactide-co-glycolide); poly(hydroxybutyrate); poly(hydroxybutyrate-co-valerate); polydioxanone; polyorthoester; polyanhydride; poly(glycolic acid); poly(D,L-lactic acid); poly(glycolic acid-co-trimethylene carbonate); polyphosphoester; polyphosphoester urethane; poly(amino acids); cyanoacrylates; poly(trimethylene carbonate); poly(iminocarbonate); copoly(ether-esters) (e.g. PEO/PLA); polyalkylene oxalates; polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid; polyurethanes; silicones; polyesters; polyolefins; polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins; polyurethanes; rayon; rayon-triacetate; cellulose; cellulose acetate; cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

[0044] The Figures have not been drawn to scale, and the dimensions such as depth and thickness of the various regions and layers have been over or under emphasized for illustrative purposes. Referring to Figures 1A and 1B, a stent 10 is formed from a plurality of struts 12. Struts 12 are separated by gaps 14 and may be interconnected by connecting elements 16. Struts 12 can be connected in any suitable configuration and pattern. Stent 10 is illustrated having an outer surface 18 (tissue-contacting surface) and an inner surface 20 (blood-contacting surface). A hollow, central bore 22 extends longitudinally from a first end 24 to a second end 26 of stent 10.

[0045] Figure 2 illustrates stent 10 having a first coating 28 formed on inner surface 20. First coating 28 can be of any suitable thickness. The thickness of first coating 28 can be from about 0.1-15 microns, more narrowly from about 3 microns to about 8 microns. By way of example, first coating 28 can have a thickness of about 5 microns.

[0046] First coating 28 can be made from a polymeric material containing an angiogenic substance. First coating 28 can be formed by any suitable method, such as by applying a first solution containing a dissolved mixture of a first solvent, a first polymer, and the angiogenic substance onto inner surface 20 and allowing the first solvent to evaporate from the first solution. Examples of suitable solvents include dimethylsulfoxide (DMSO), chloroform, acetone, water (buffered saline), xylene, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, ethyl acetate, methylethylketone, propylene glycol monomethylether, isopropanol, isopropanol admixed with water, N-methyl pyrrolidinone, toluene, and combinations thereof.

[0047] The first solution can be deposited onto inner surface 20 in any suitable manner capable of allowing the first solution to be applied to inner surface 20 without exposure of outer surface 18 to the first solution. For example, outer surface 18 can be covered by a removable sheath during application of the first solution, allowing the first solution to coat only inner surface 20.

[0048] The dosage or concentration of the angiogenic substance required to produce a therapeutic effect should be less than the level at which the angiogenic substance produces toxic effects and greater than the level at which non-therapeutic results are obtained. The dosage or concentration of the angiogenic substance required can depend upon factors such as the particular circumstances of the patient; the time over which the angiogenic substance administered resides at the treatment site; and if other bioactive substances are employed, the nature and type of the substance or combination of substances. Standard pharmacological test procedures to determine dosages are understood by one of ordinary skill in the art.

[0049] Figure 3 illustrates stent 10 coated in accordance with another embodiment of the present invention. In addition to first coating 28 containing an angiogenic substance on inner surface 20, a second coating 32 containing a therapeutic substance is formed on outer surface 18 of stent 10. Second coating 32 can be of any suitable thickness. The thickness of second coating 32 can be from about 0.1-15 microns, more narrowly from about 3 microns to about 8 microns. By way of example, second coating 32 can have a thickness of about 4 microns.

[0050] Second coating 32 can be formed on outer surface 18 prior to or subsequent to the formation of first coating 28 on inner surface 20. Stent 10 can be temporarily mounted on a conventional mandrel such that the mandrel fits within hollow bore 22 and against inner surface 20 or first coating 28. Stent 10 can then be immersed in or sprayed with a polymer-solvent composition containing a therapeutic substance to form second coating 32.

[0051] The therapeutic substance in second coating 32 can be an angiogenic substance that is the same as or different than the angiogenic substance contained within first coating 28. Alternatively, the therapeutic substance in second coating 32 can be any active ingredient capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. The therapeutic substance can also be for enhancing wound healing in a vascular site and improving the structural and elastic properties of the vascular site. More particularly, the therapeutic substance should be for inhibiting abnormal migration and/or proliferation of smooth muscle cells for the treatment of restenosis. Examples of such substances include antiproliferative, antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antioxidant and anti-migratory substances, inhibitors of matrix synthesis, and combinations thereof.

[0052] A suitable example of an antiproliferative substance is actinomycin D, or derivatives and analogs thereof. Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. Examples of suitable antineoplastics include paclitaxel and docetaxel. Examples of suitable antiplatelets, anticoagulants, antifibrins, and antithrombins include sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of suitable antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mitomycin. Examples of suitable cytostatic or antiproliferative agents include angiopeptin (a somatostatin analog from Ibsen), angiotensin converting enzyme inhibitors such as CAPTOPRIL (available from Squibb), CILAZAPRIL (available from Hoffman-LaRoche), or LISINOPRIL (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonist, LOVASTATIN (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available form Glazo), Surmin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, and dexamethasone.

[0053] Figures 4A-4B illustrate stent 10 in accordance with another embodiment of the present invention. In lieu of, or in addition to, coating outer surface 18 and inner surface 20 with polymeric coatings, cavities 34a and/or 34b are disposed in surfaces 18 and 20, respectively, for releasably containing the therapeutic and/or angiogenic substances. Cavities 34a within outer surface 18 contain a therapeutic substance, as indicated by dotted region 36, and cavities 34b within inner surface 20 contain an angiogenic substance, as indicated by dotted region 38. The substances can be deposited into the cavities in a solid form or contained in a polymeric matrix for reducing the rate of release.

Using the Embodiments of the Device to Treat Ischemia

[0054] Figures 5A-5D illustrate the use of stent 10 in a vessel 40 through which blood flows in a downstream direction 42. Vessel 40 is illustrated having an occlusion 44 and an ischemic region 46 downstream of occlusion 44. Referring to Figure 5A, stent 10, carrying an angiogenic substance within a first coating on inner surface 20 and/or in cavities 34b within inner surface 20, is positioned within vessel 40 at a location that is upstream of, or proximal to, occlusion 44. In one such embodiment, stent 10 is made of a bioabsorbable material. As indicated by dashed arrows 48 in Figure 5B, the angiogenic substance is released from inner surface 20 into blood flowing through central bore 22 in the downstream direction 42. The angiogenic substance, as illustrated by dotted region 38 in Figure 5C, emerges from the distal end of stent 10, flowing in the downstream direction 42 toward and through occlusion 44.

[0055] Referring to Figure 5D, the released angiogenic substance can stimulate or promote formation of one or more collateral vessels 50 downstream of, or distal to, the site of implantation of stent 10. Such arteriogenesis enables circumvention of occlusion 44 by providing an alternate, less resistant pathway through which blood may travel. Accordingly, blood flow to ischemic region 46 is increased as blood travels through collateral vessel 50 as well as through occluded vessel 40.

[0056] The angiogenic substance can also stimulate angiogenesis downstream of the site of implantation of stent 10. Microvessels can provide blood with an increased number of pathways. Blood flow to ischemic region 46 can be therefore increased in primarily two ways. First, the increased number of pathways through which blood may flow can result in an increase in the amount of blood that reaches ischemic region 46. Second, an increased capillary bed in the ischemic region will allow more efficient distribution of blood in this zone and will result in a decreased overall resistance of this bed. Such a decrease in pressure may allow more blood to travel through vessel 40 due to a lower resistance therein.

[0057] Stent 10 can optionally provide for the release of a therapeutic substance carried within second coating 32 on outer surface 18 and/or in cavities 34a within outer surface 18, as illustrated by arrows 52. In an embodiment in which the therapeutic substance is a second angiogenic substance, the second angiogenic substance can stimulate formation of additional collateral vessels 50 as well as additional microvessels. Alternatively, in an embodiment in which the therapeutic substance is a non-angiogenic substance, the therapeutic substance can otherwise act at the site of implantation of stent 10 for the treatment of vessel 40. By way of example, in an embodiment in which the therapeutic substance is an anti-proliferative substance, e.g., actinomycin D, the substance can help inhibit abnormal migration or proliferation of smooth muscle cells at the site at which stent 10 was implanted.

[0058] Referring to Figure 6, stent 10 may be used to mechanically dilate vessel 40 in addition to providing treatment via the release of an angiogenic substance and an optional second therapeutic substance. Stent 10 can be positioned within vessel 40 such that stent 10 extends at least partially through occlusion 44. Stent 10 can physically hold open the wall of vessel 40 at the site of implantation. Accordingly, blood can flow more freely through the previously-occluded portion of vessel 40 in the downstream direction 42 toward ischemic region 46.

[0059] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

CLAIMS

What is claimed is:

1. A stent, comprising:

a tubular body having an outer surface for contacting the wall of a vessel and an inner surface;

a first coating supported by said inner surface and containing an angiogenic substance for the release of said angiogenic substance in said vessel; and

a second coating supported by said outer surface and containing a therapeutic substance for applying said therapeutic substance to said wall of said vessel.

2. The stent of Claim 1, wherein said first coating is different than said second coating.

3. The stent of Claim 1, wherein said therapeutic substance is selected from a group of antiproliferative, antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antioxidant, and anti-migratory substances, inhibitors of matrix synthesis, and combinations thereof.

4. The stent of Claim 1, wherein said angiogenic substance is selected from a group of vascular endothelial growth factor (VEGF) in any of its multiple isoforms, fibroblast growth factors, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor beta (TGF-beta) in any of its multiple isoforms, transforming growth factor alpha (TGF-alpha), lipid factors, hypoxia-inducible factor 1-alpha (HIF-1-alpha), PR39, del 1, nicotine, insulin-like growth factors, placental growth factor (PlGF), hepatocyte growth factor (HGF), estrogen, follistatin, proliferin, prostaglandin E1, prostaglandin E2, cytokines, tumor necrosis factor (TNF-alpha), erythropoietin, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), angiogenin, hormones, and genes that encode such substances.

5. A stent for implanting in a blood vessel comprising a tubular structure having an inner surface and an outer surface, comprising:

a first therapeutic substance carried by the inner surface for being released downstream with the flow of blood; and

a second therapeutic substance, different from the first therapeutic substance, carried by the outer surface for application to the blood vessel wall,

wherein the first therapeutic substance facilitates therapeutic angiogenesis and wherein the second therapeutic substance inhibits migration or proliferation of smooth muscle cells.

6. The stent of Claim 5, wherein the inner surface has a first polymeric coating deposited thereon for the sustained release of the first therapeutic substance and wherein the outer surface has a second polymeric coating deposited thereon for the sustained release of the second therapeutic substance.

7. The stent of Claim 5, wherein the inner surface comprises a plurality of cavities for releasing the first therapeutic substance when exposed to the flow of blood.

8. The stent of Claim 5, wherein the inner surface comprises a plurality of cavities for releasing the first therapeutic substance when exposed to the flow of blood and wherein the outer surface comprises a plurality of cavities for applying the second therapeutic substance to the blood vessel wall.

9. The stent of Claim 5, wherein the first therapeutic substance is selected from a group of vascular endothelial growth factor (VEGF) in any of its multiple isoforms, fibroblast growth factors, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor beta (TGF-beta) in any of its multiple isoforms, transforming growth factor alpha (TGF-alpha), lipid factors, hypoxia-inducible factor 1-alpha (HIF-1-alpha), PR39, del 1, nicotine, insulin-like growth factors, placental growth factor (PlGF), hepatocyte growth factor (HGF), estrogen, follistatin, proliferin,

prostaglandin E1, prostaglandin E2, cytokines, tumor necrosis factor (TNF-alpha), erythropoietin, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), angiogenin, hormones, and genes that encode such substances.

10. The stent of Claim 5, wherein the second therapeutic substance is selected from a group of actinomycin D, docetaxel and paclitaxel.

11. A method for increasing blood flow to ischemic tissues located downstream from an occluded region in a blood vessel, comprising:

implanting a stent in the blood vessel at a location upstream from the ischemic tissues, the stent having an inner surface carrying an angiogenic substance.

12. The method of Claim 11, wherein the stent is implanted at a location upstream of the occluded region.

13. The method of Claim 12, wherein the stent is made of a bioabsorbable material.

14. The method of Claim 11, wherein the stent is implanted across at least a portion of the occluded region.

15. The method of Claim 11, wherein the inner surface supports a coating containing the angiogenic substance.

16. The method of Claim 11, wherein the inner surface includes cavities containing the angiogenic substance.

17. The method of Claim 11, wherein the angiogenic substance is selected from a group of vascular endothelial growth factor (VEGF) in any of its multiple isoforms, fibroblast growth factors, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor beta (TGF-beta) in any of its multiple isoforms, transforming growth factor alpha (TGF-alpha), lipid factors, hypoxia-inducible factor 1-alpha (HIF-1-alpha), PR39, del 1, nicotine, insulin-like growth factors, placental growth factor (PlGF), hepatocyte growth factor (HGF), estrogen, follistatin, proliferin, prostaglandin E1, prostaglandin E2, cytokines, tumor necrosis factor (TNF-alpha), erythropoietin, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), angiogenin, hormones, and genes that encode such substances.

18. The method of Claim 11, wherein the stent additionally includes a coating disposed on the outer surface of the stent, the coating carrying a therapeutic substance.

19. The method of Claim 18, wherein the therapeutic substance is selected from a group of actinomycin D, docetaxel and paclitaxel.

20. The method of Claim 11, wherein the stent comprises cavities on the outer surface containing a therapeutic substance.

21. The method of Claim 11, wherein the blood vessel is located in mammalian coronary vasculature.

22. The method of Claim 11, wherein the blood vessel is located in mammalian peripheral vasculature.

STENT FOR INCREASING BLOOD FLOW TO ISCHEMIC TISSUES AND A METHOD OF USING THE SAME

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ABSTRACT

Stents and a method of using the stents to increase blood flow to ischemic tissues in a patient are disclosed.